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PERFORATION OF THE ILEUM FOLLOWING LATE ILEOSTOMY FOR ULCERATIVE COLITIS*

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THE treatment of intractable, chronic, nonspecific ulcerative colitis by surgery in the form of ileostomy has been advocated in recent years by many surgeons as a means of arresting the disease. McKittrick and Miller,[1] Lahey,[2] Cave,[3] Jones[4] and others have reported marked success with this operation, but each has been careful to point out that when employed in the terminal stages, ileostomy is accompanied by an extremely high mortality rate. The present paper is a report of 2 cases illustrating a hitherto undescribed complication of late ileostomy for ulcerative colitis.

Both cases presented are similar in that death was due to generalized peritonitis following perforation of an ulcerative lesion of the ileum. In each case the perforation occurred above the site of ileostomy, the points of perforation being 15 and 6 cm., respectively, above the ileostomy openings. Grossly, the terminal ileum in each case showed a diffuse ulcerative process similar to that seen in the colon. The ulcers in the ileum were sharply demarcated and varied in size and shape, and the intervening mucosa was swollen. Microscopically, the mucosa was absent or necrotic, and there was edema and thickening of the submucosa, together with marked polymorphonuclear leukocytic and lymphocytic infiltration of the submucosa and of the mucosa at the ulcer edge. In the deep ulcers there was similar leukocytic infiltration of the muscularis. The pathologic findings, in other words, were identical with those found in the colon in chronic ulcerative colitis.

Because of the frequency with which the disease process extends into the terminal ileum in the later stages of the disease, the question arises whether in the present cases the disease process did not exist in the ileum above the site elected for enterostomy at the time of operation. This question is reasonable because in each case ileostomy was performed close to the ileocecal valve. Certainly the perforations were not related directly to the ileostomies, since these patients lived seven weeks and eight and a half weeks, respectively, after operation.

Supportive evidence that disease existed proximal to the site of ileostomy before operation in each of these patients was the early postoperative course, for the ileostomy drainage never became solid but remained liquid and profuse. This was in marked contrast to the early postoperative course of other treated patients who survived, for in these cases the drainage began to solidify by the end of the second postoperative week. In addition, in Case 2, old healed ulcers were found in the terminal ileum above the ileostomy at autopsy.

Extension of nonspecific ulceration of the terminal ileum in patients suffering from chronic ulcerative colitis is fairly well known but has not received sufficient emphasis. In order to determine the frequency of this lesion in the ileum, 16,500 consecutive autopsies from the files of the Mallory Institute of Pathology, Boston City Hospital, were reviewed. Including the present cases, there were 44 cases in which chronic ulcerative colitis was considered to be the primary cause of death. In 17 of these, or 39 per cent, there was involvement of the small intestine. In the majority of cases the ulcerative process was confined to the terminal ileum — that is, to the lower 30 cm. of the ileum. In 3 cases, however, the ulcers extended throughout the lower third of the ileum. The incidence of perforation was striking. There was perforation of the colon in 7 cases (16 per cent), whereas perforation occurred in lesions of the small intestine in the 2 operative cases described and in 2 other cases in which fistulas developed from ulcers in the terminal ileum and jejunum. In other words, the incidence of perforative lesions of the small bowel in cases in which there was ulcerative ileitis was 24 per cent, or one and a half times greater than the incidence of perforative lesions of the large bowel.

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It is evident from a study of this material that the danger of perforation in the terminal ileum is always present in cases of severe ulcerative colitis in which surgery is delayed. To reduce the danger of this complication it seems wise always to do an ileostomy at least 90 cm. above the ileocecal valve and to avoid operative procedures on the terminal ileum. If a low ileostomy has been carried out and the fecal discharge remains loose and profuse, the possibility of ulceration of the terminal ileum above the ileostomy should always be kept in mind so that if acute abdominal symptoms develop, operative intervention can be immediately instituted. It should be possible in selected cases to visualize the terminal ileum before operation by barium and so to anticipate this complication.

Case Reports

Case 1. F. W. (B.C.H. 772,645), a 50-year-old, married man, was admitted to the medical service on January 8, 1935, complaining of rectal bleeding and frequent bowel movements. Three weeks before entry he began to have two to six bowel movements each day. The stools were loose and contained moderate amounts of bright-red blood. He was treated by his family physician with relief of symptoms, for 10 days. Three days before coming to the hospital, however, the symptoms returned in their original intensity and, in addition, there occurred griping pains in the lower abdomen. On the day of entry, the patient felt weak and fainted twice. He had lost approximately 20 pounds during the previous 2 months. He gave a history of rheumatic fever associated with ulcers of the rectum and frequent loose, bloody stools 6 years prior to entry.

On admission the temperature was 100.2°F., the pulse 94, the respirations 22, and the blood pressure 120/80. The patient appeared to be fairly well nourished and of normal development. There was slight generalized abdominal spasm. On rectal examination there was marked spasm of the sphincter and there was blood on the examining glove, but no masses or ulcers were palpated. The remainder of the physical examination was negative.

The patient was treated on the medical service for 23 days without success. During that time the temperature fluctuated between 99 and 103°F. and the diarrhea became severer. While the patient was on this service, large punched-out ulcers on the rectal wall were demonstrated by sigmoidoscopy on two occasions. Two barium enemas were interpreted as showing marked spasm of the sigmoid, with diminished haustral markings and multiple irregularities of the transverse and sigmoid colon. In addition, there was a constant filling defect of the cecum.

On the 23rd hospital day, the patient was transferred to the Fifth Surgical Service for ileostomy. This was performed under spinal anesthesia on the day of transfer. At operation, the cecum and colon were found to be thickened and hyperemic. The external appearance of the terminal ileum was not noteworthy. A loop ileostomy was performed approximately 7 cm. proximal to the ileocecal valve. The patient withstood the operation well. During the next 5 days he continued to have diarrhea and began to suffer from crampy abdominal pains and vomiting. On the 5th postoperative day, the loop of the ileum was opened. Vomiting continued and the blood chlorides became depleted. This was corrected by administering intravenously large amounts of normal saline solution. The vomiting gradually decreased and the temperature gradually returned to normal, so that by the 34th postoperative day it was believed that the patient was definitely improved; however, the ileostomy discharge continued to be loose and the patient had occasional bloody movements by rectum.

On the 56th postoperative day, the patient again began to suffer from severe abdominal cramps and vomiting. His condition became progressively worse, and he died on the 60th postoperative day.

Laboratory studies during the hospital stay showed the red-cell count to be 3,000,000 and the hemoglobin 60 per cent. The white-cell count varied between 10,100 and 16,700, with 70 per cent neutrophils, 17 per cent lymphocytes, 2 per cent monocytes and 1 per cent basophils. The blood-cell morphology was not remarkable. Repeated urine examinations showed traces of albumin and many white cells, and two specimens contained red cells. A blood Kahn test was negative. The skin reactions to 1:10,000, 1:1000 and 1:100 dilutions of tuberculin were negative. Agglutination tests against typhoid, paratyphoid and Brucella organisms were negative. Two blood cultures showed no growth. The stools were always guaiac positive, and microscopic examination revealed no ova or parasites. Repeated cultures of the stools were negative for pathogenic organisms. A biopsy of a rectal ulcer showed chronic inflammation.

Autopsy (35–202). At autopsy the body was that of a poorly nourished man. In the right lower quadrant, at the level of the anterosuperior spine of the ileum, were two openings in the anterior abdominal wall, each 3 cm. in diameter and each containing an open end of ileum. Throughout the peritoneal cavity 800 cc. of thick, bright-green, foul-smelling, purulent matter was found. Many loops of small intestine were matted together by fibrin, and in addition, other loops of small bowel were adherent to the ascending and descending colon and to the bladder and rectum. The small intestine was moderately distended. Twenty-five centimeters above the ileocecal valve and 15 cm. above the ileostomy wounds were two round perforations in the wall of the ileum, each approximately 1 cm. in diameter. Beginning at a point 60 cm. above the ileocecal valve and extending throughout the entire colon and rectum, there was marked ulceration of the mucosa of the bowel. The ulcers varied in size, were clearly defined and irregular in outline and had ragged, gray-black bases. In many areas the mucosa had been undermined, leaving bands of mucosa without attachment to underlying tissue. In some areas the ulcers were confluent so that the bowel wall was denuded of mucosa for a distance of 7 to 10 cm. The ulceration appeared to be of equal severity throughout the colon, but at the points of perforation in the ileum it was especially severe.

Sections of the ileum showed the serosa to be partially covered by an exudate consisting chiefly of fibrin and polymorphonuclear leukocytes. The mucosa was ulcerated, and this process extended into the muscularis. The mucosa and the muscularis were diffusely infiltrated by plasma cells and lymphocytes. Sections of the colon showed extensive ulceration of the mucosa and muscularis, with marked plasma-cell and lymphocytic infiltration.

Cultures of ulcers in the ileum and from the peritoneal cavity showed *Escherichia coli*, alpha-hemolytic and beta hemolytic streptococci and *Proteus vulgaris*. Type 8 pneumococcus was cultured from the heart's blood.

In addition to the lesions described, the patient was found to have bronchopneumonia of both lower lobes and pulmonary congestion and edema.

The anatomic diagnoses were ulcerative colitis, ulcerative ileitis with perforation, generalized peritonitis, bronchopneumonia, and pulmonary congestion and edema.

Case 2. H. S. (B.C.H. 987,922), a 44-year-old, married woman, was admitted to the medical service on June 25, 1940, complaining of bloody diarrhea of 10 months' duration. She stated that she had had from fifteen to twenty stools every twenty-four hours, and that the stools had invariably contained bright blood and occasionally mucus. In addition, she suffered from crampy pains in the umbilical region. She estimated that she had lost 20 pounds in weight during the course of her illness.

Physical examination on admission revealed a normally developed, poorly nourished, excitable woman who gave the appearance of being chronically ill. The temperature was 100°F., the pulse 100, the respirations 16, and the blood pressure 125/85. The left eardrum was perforated. There was a short systolic precordial murmur. There was an old laceration of the cervix.

The patient was placed on a high-vitamin, low-residue diet, supplemented by various vitamin preparations. Paregoric, bismuth subcarbonate and belladonna were given, with a moderate decrease in the diarrhea. Proctoscopy showed multiple undermined ulcer craters with dirty-gray bases, which bled easily. Scrapings from the craters were negative for amebas. The patient was given sulfathiazole, without improvement, and because she developed toxic symptoms this drug was discontinued. Since all efforts to control the

diarrhea were unsuccessful and the patient was obviously failing, she was transferred to the Fifth Surgical Service on the 59th day for ileostomy. At the time of transfer there was a foul, purulent vaginal discharge from a rectovaginal fistula.

Ileostomy was performed on the day of transfer under intravenous Pentothal Sodium anesthesia. The terminal ileum was divided 15 cm. from the ileocecal valve, and the distal end was brought through a separate stab wound in the McBurney area. At that time the serosal surface of the terminal ileum appeared normal.

The patient's postoperative condition was poor. The temperature was 102.4°F., the pulse 120, and the respirations 22. There was a persistent, profuse discharge from the ileostomy wound. Large quantities of normal saline solution were administered intravenously, and fourteen blood transfusions were given in an effort to maintain the total serum protein and hemoglobin, which averaged 4.5 gm. and 65 per cent, respectively.

Two weeks postoperatively, the patient developed severe, cramplike abdominal pains and began to vomit. The ileostomy drainage temporarily ceased. She was placed on Wangensteen drainage and responded well, so that in 2 days all signs of obstruction had disappeared. Starting with the 4th postoperative week, her appetite became progressively poorer and it was necessary at times to resort to forcible feeding through an inlying Levine tube. Large doses of thiamine chloride and ascorbic acid were given daily.

During the 6th postoperative week, the patient developed signs of acute pericarditis, and this diagnosis was confirmed by x-ray. Purulent material was obtained on aspiration of the pericardium, and on culture of this material *Staphylococcus aureus*, fusiform bacilli and *Clostridium welchii* were obtained. Pericardiostomy was immediately performed. The patient remained in shock for 24 hours in spite of all supportive treatment, which included transfusions of 1700 cc. of blood. At that time she also developed a panophthalmitis of the right eye. During the following 6 days the patient recovered from shock. The pericardial cavity was irrigated regularly. On the afternoon of the 6th day following pericardiostomy, the 49th day following ileostomy, she suddenly complained of pain in the right lower quadrant of the abdomen. Examination of this area showed tenderness and spasm. The pulse and respirations rose rapidly, the patient's condition generally deteriorated, and she died 12 hours later.

Autopsy (40–828). At autopsy the body was that of an emaciated woman. There was a recent open operative wound over the heart measuring 11 by 4 cm. Portions of the 5th and 6th ribs had been removed, leaving a window 4 by 4 cm., opening directly into the pericardial cavity. There was a well-healed scar of the right rectus muscle, as well as a healed ileostomy scar on the right. There was a patent ileostomy in the midline. When the peritoneal cavity was examined, the omentum was adherent to the ileum at a point 6 cm. above the ileostomy wound. A small perforation was found in the wall of the ileum at that point, and the serosal surfaces were covered with thick, fibropurulent exudate. There was 500 cc. of cloudy fluid flecked with fibrin in the lower abdomen and pelvis. *Staph. aureus* and alpha-hemolytic streptococci were cultured from this fluid. There were no further adhesions, either old or recent, in the peritoneal cavity. The distal stump of the ileostomy was well healed and was 8 cm. above the ileocecal valve.

The esophagus, stomach, duodenum, jejunum and proximal portion of the ileum were normal. Beginning at a point 15 cm. above the ileostomy were a series of approximately fifteen small ulcerated areas in the mucosa. These mucosal lesions had an irregular, punched-out appearance, and each measured approximately 4 mm. in circumference. There were a few dense white scars that apparently represented healed ulcers. One of the active ulcers had perforated as described above. The ileum distal to the ileostomy contained a few ulcers similar to those already described.

Sections of ulcers from the ileum showed areas from which the mucosa had sloughed. The intact mucosa at the edge of the ulcers and the muscularis underlying the base of the ulcer were infiltrated by lymphocytes and plasma cells.

Ulcerations were found in the ascending colon and rectum. The ulcers in the rectum were large and tended to coalesce so that large areas were denuded of mucosa, leaving the muscularis bare. Sections showed necrosis and sloughing of the mucosa. There was marked infiltration of the remaining mucosa by lymphocytes and plasma cells. These lesions were much severer than those seen in the ileum. *Esch. coli* and *Pseudomonas aeruginosa* were cultured from these ulcers. The rectum and vagina were adherent in places, and there were two small fistulas between these organs.

The epicardial and parietal pericardial surfaces were smooth but dull and nonglistening. There were no adhesions or grossly purulent matter. Sections showed some thickening of the epicardium and pericardium by granulation tissue, together with a small amount of necrotic débris and a few bacteria.

In addition to the above lesions there was moderate atelectasis and a slight amount of bronchopneumonia in the right lower lobe.

The anatomical diagnoses were ulcerative colitis, ulcerative ileitis with perforation, peritonitis, purulent pericarditis (healing), pyohemothorax (left), atelectasis (left lower lobe), bronchopneumonia (left lower lobe) and rectovaginal fistulas.

Summary

Two cases are described in which perforation of the ileum above the site of ileostomy with resulting peritonitis occurred following operation.

It is suggested that, in cases of prolonged severe ulcerative colitis, ileostomy, if indicated, be performed at least 90 cm. above the ileocecal valve.

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ACUTE PERICARDITIS SIMULATING MYOCARDIAL INFARCTION*

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THE occurrence of pericarditis in association with rheumatic fever, myocardial infarction, tuberculosis, pneumonia, septicemia, generalized lupus and uremia is well known and usually creates no diagnostic problems. Acute pericarditis unassociated with these diseases has, however, been recognized.[1] These cases may be characterized by pain similar to that which occurs in acute myocardial infarction, necessitating the exercise of great care in differential diagnosis. This is of more than academic importance, since the treatment and prognosis of the two disorders are markedly different. During the past year 5 cases of this type of pericarditis were seen, and in 4 of them a mistaken diagnosis of acute myocardial infarction had been made. Those points that have been found most helpful in achieving a correct diagnosis will be discussed below.

CASE REPORTS

CASE 1. S. B., a 30-year-old, married man, was seen in another hospital on September 19, 1942. While convalescing from an attack of virus pneumonia, he was awakened at 1:30 a.m. on the day of admission by severe, constricting pain in the anterior chest and sharp precordial pain, markedly accentuated by bodily movements and inspiration. When he was examined within a few hours by his physician, a loud pericardial friction rub was heard. The pain was so severe and persistent that morphine had to be administered subcutaneously for relief.

Physical examination on admission revealed a loud pericardial friction rub over the entire precordial area, diminished respiratory excursion of the left lower chest and a blood pressure of 142/76. The friction rub was constantly audible during the first 15 days. Daily swings in temperature up to 104°F. occurred for 12 days, and the pulse rate averaged 85. The white-cell count was usually normal, but on one occasion reached 14,300. Electrocardiograms were consistent with acute pericarditis and at no time showed the pattern of myocardial infarction. Several teleroentgenograms revealed considerable cardiac dilatation, with subsequent reversion to normal size, and small pleural effusions. Fluoroscopy showed normal ventricular pulsations.

Sulfadiazine was administered in adequate doses both before and after admission, but was without benefit and was therefore discontinued. The patient rapidly improved and was discharged on the 32nd day.

CASE 2. M. D., a 29-year-old, unmarried woman, entered the Beth Israel Hospital on January 2, 1943. At the age of 9 or 10 she had had pain and swelling in all the joints, and since then stiffness and swelling of the fingers and ankles. She was nervous and unstable and occasionally noted coldness and blanching of the fingertips. There were no skin lesions or sensitivity to sunlight.

The present illness began 4 days before admission with the gradual onset of dull, gnawing pain at the top of the left shoulder, becoming severe on motion or deep inspiration. Dyspnea developed and increased to such an extent that the patient was comfortable only when lying on several pillows. Two days before entry crushing pain in the precordial and substernal areas developed. It became extremely severe on the following day and was accompanied by marked sweating and respiratory distress.

Physical examination revealed pallor of the skin, profuse perspiration, marked respiratory distress and cyanosis of the lips and fingertips. The pharynx was injected. The heart was of normal size, and a loud, leathery, pericardial friction rub was heard. The white-cell count was 10,000 to 11,000, and the corrected sedimentation rate (Rourke–Ernstene method) on admission was 1.3 mm., gradually falling to 0.70 mm. The reaction to an intradermal tuberculin test in a dilution of 1:1000 was positive. Seven electrocardiograms showed the classic pattern and evolution of acute pericarditis, but none of the features of myocardial infarction. Three teleroentgenograms and fluoroscopic examination showed a normal-sized heart with normal pulsations and a small pleural effusion on the left, which subsequently disappeared. All symptoms subsided by the 2nd day, but the friction rub was still audible on the 3rd day. The heart sounds were normal and there were no murmurs. The temperature was elevated as high as 100.5°F. for the first 8 days, and the pulse rate was 75.

The patient was discharged on the 13th day. Two minor recurrences of short duration took place within the next 6 months.

CASE 3. N. B., a 32-year-old, unmarried man, previously in good health, was awakened at 6 a.m. on June 28, 1943, by severe substernal pain that radiated to the left shoulder and arm. When seen by his physician within half an hour after the onset of the attack, he was sweating profusely, appeared apprehensive, and was in severe pain. The pain was not helped by sublingual nitroglycerin, but was slightly relieved by the subcutaneous administration of ¼ gr. of morphine sulfate. The systolic blood pressure was 90. A loud pericardial friction rub was audible. The patient soon became pulseless, and the blood pressure could not be measured. An hour later the systolic blood pressure was 100 mm. and the patient was sent to the Beth Israel Hospital by ambulance. The pain soon disappeared following several injections of morphine sulfate.

Except for several minor recurrences during the hospital stay, the clinical course was uneventful. The pericardial friction rub was audible for 4 days. The blood pressure remained normal. The white-cell count on admission was 16,000, but 2 days later was normal. The corrected sedimentation rate was 0.8 mm. per minute. The temperature was normal throughout, and the pulse rate averaged 60 to 70. Five electrocardiograms were taken, the first one several hours after the onset of the attack. They presented the usual characteristics of acute fibrinous pericarditis, but none of the features associated with acute myocardial infarction.

The patient was discharged on the 19th hospital day.

CASE 4. P. N., a 41-year-old, married man, entered the Beth Israel Hospital on July 11, 1943. He had been well until the previous December, when squeezing substernal pain suddenly began while he was walking home in a snowstorm. He felt "grippy" and noted that the pain was aggravated by inspiration. The pain rapidly became severe, and when he reached home he summoned his physician, who made a diagnosis of pleurisy. The pain lasted 2 hours, but recurred off and on during the next 10 days. The patient remained in bed for 1 week. Following this episode, exertion, especially walking up an incline, provoked squeezing, high substernal pain, with radiation down the right arm and occasionally down the left arm. Relief was afforded by resting for about a minute. Nevertheless, he continued to be extremely active.

Three days before admission, the patient again felt "grippy" and had a chill, followed almost immediately by severe, crushing pain in the anterior chest radiating to both arms, as well as by cough and dyspnea. The pain, intensified by inspiration and by turning on the side, was at first intermittent, but became constant on the day of entry and remained so for the first 4 or 5 days, requiring repeated subcutaneous injections of morphine sulfate for relief.

Physical examination at the time of admission revealed a dyspneic, disoriented, cyanotic man with profuse sweating, a loud pericardial friction rub over the entire precordial area and crepitant rales throughout both lungs. The blood pressure was

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at first normal, but soon dropped to 70/50. There was no distention of the neck veins, enlargement of the liver or edema. The temperature during the first 5 days ranged as high as 104.2°F. falling abruptly to normal on the 5th day. The pulse rate averaged 115 during the febrile period and then 70 to 80. With the fall in temperature, the improvement in the clinical picture was dramatic; the pain, dyspnea, circulatory collapse and disorientation disappeared. The lungs were clear, but the friction rub remained loud for 10 days, and then gradually diminished until it was barely audible.

On the 14th day the patient was awakened by severe substernal pain, radiating to both arms, of 30 minutes' duration. The skin became cold and clammy, and the friction rub was again intensely loud. On the 19th day he had a shaking chill, followed by a slight rise in temperature. Pleural friction rubs appeared on both sides of the chest, and diminished breath sounds and a few rales at the lung bases. Squeezing substernal pain recurred frequently, always aggravated by turning in bed or by inspiration, until the 22nd day, at which time the friction rub disappeared. Thereafter convalescence was uneventful.

The initial white-cell count was 23,300, and later the same day it was 19,450. Subsequently it fluctuated between 8900 and 17,400, and was 15,000 the day before discharge. The corrected sedimentation rate was 1.2 mm. per minute. Hinton and Kahn blood reactions were negative, and an intradermal tuberculin test in a dilution of 1:1000 was weakly positive. The arm-to-tongue circulation time 2½ weeks after admission was 17 seconds. Eight electrocardiograms, including multiple chest leads, were consistent with a diagnosis of acute pericarditis and at no time showed any of the features of acute or old myocardial infarction. An x-ray film of the chest taken on admission showed a small heart and moderately severe pulmonary congestion. X-ray examination on the 9th and 15th days revealed considerable and progressive dilatation of the heart, clear lung fields, thickened pleura and a small amount of pleural fluid. Two subsequent x-ray examinations disclosed a progressive diminution in heart size. Careful fluoroscopic study showed no evidence of pericardial effusion or of localized abnormalities of ventricular pulsation.

The patient was discharged on the 32nd day.

Case 5. O. M., a 68-year-old retired salesman, entered the Beth Israel Hospital on July 21, 1943. At the age of 19 he had had a urethral discharge and a penile sore. For the last 20 years he had had severe perennial bronchial asthma, which had required frequent subcutaneous injections of adrenalin. The present illness began 5 days before admission with the sudden onset of low substernal and precordial pain, radiating to the left side of the chest posteriorly. It rapidly became extremely severe and crushing and was markedly intensified by inspiration and coughing. The patient felt weak and went to bed. Half an hour following an injection of morphine, the pain began to abate, and on the 3rd day, although still present, was so mild that he was able to resume his usual activities. On the day before admission the pain recurred, but was severer than it was during the first attack.

The important physical findings were clubbing and cyanosis of the fingers, asthmatic breathing and a normal blood pressure. The loud asthmatic breathing obscured the heart sounds. The temperature on admission was 101°F. and remained slightly elevated for the first 11 days. The pulse rate averaged 90. The white-cell count was normal, but the sedimentation rate was elevated. Hinton and Kahn blood reactions were negative. Nine electrocardiograms displayed the classic pattern of acute pericarditis, starting with elevations of the RS-T segment in all the leads, with subsequent inversion of the T waves in all leads and rapid reversion to a normal pattern; the Q-T pattern of myocardial infarction did not appear. Three teleroentgenograms showed a normal-sized heart and bilateral pleural thickening at first, followed by a small pleural effusion on both sides. There was no mediastinal emphysema or pneumothorax. Fluoroscopy revealed normal cardiac pulsations.

Adrenalin was administered subcutaneously for the asthma, without any intensification of the pain, which completely subsided by the 5th day. Following an uneventful convalescence, the patient was discharged on the 15th day.

Clinical Features

The most striking symptom in the type of pericarditis here discussed is substernal and precordial pain, either localized in these regions or with radiation to the shoulders, arms and back. It is moderate or severe and is described as squeezing, constricting, crushing or sharp. Bodily movement, cough and inspiration invariably accentuate the pain from its very onset. At first it may be intermittent, but it always becomes constant and lasts for hours or days. In some cases, preceding or simultaneously with the onset of pain, there is evidence of a respiratory infection or a "grippy" feeling, with or without chilliness or a chill. The onset may occur during recovery from a respiratory infection. In other cases there is an abrupt onset, with no indication of any antecedent illness. Respiratory distress or dyspnea is frequent, and weakness or circulatory collapse may ensue. Profuse perspiration almost always occurs, and the patient may be apprehensive or disoriented. Examination reveals a loud pericardial friction rub, as a rule at the first examination, and it is constantly present for a few days to two weeks. Usually it is heard over the entire precordial area. In some cases the heart becomes moderately or markedly dilated, subsequently returning to normal size. Involvement of the pleura, demonstrated by the finding of a pleural friction rub or thickened pleura and a small pleural effusion on x-ray examination, may occur. Pulmonary congestion or infection may give rise to various lung signs, but evidence of frank congestive failure is absent. The blood pressure may fall to shock levels; in rare cases it is unobtainable.

In some cases the temperature is normal, but as a rule it is elevated at the onset, later reaching a level of 103 to 104°F. or occasionally higher and persisting as long as ten days. The pulse rate is slow in relation to the temperature elevation and in some cases is strikingly slow and irregular (sinus arrhythmia). Paroxysmal rapid heart action may occur. The sedimentation rate is always rapid, but the white-cell count may be normal. When the latter is elevated, it may be as high as 25,000 and may fluctuate markedly from day to day. Electrocardiograms reveal the pattern of acute pericarditis, but never the features of acute myocardial infarction. Fluoroscopy discloses a normal heart or a dilated heart with diminished cardiac pulsations, but no localized diminution, absence or reversal of pulsation.

This clinical picture does not, of course, occur in its complete form in every case of pericarditis. There may be no pain or only sharp, stabbing, precordial and left-shoulder pain of slight or moderate intensity. In such cases no confusion with myocardial infarction should present itself.

Differential Diagnosis

It is obvious from consideration of the above-described clinical picture that acute fibrinous pericarditis may closely simulate acute cardiac infarction. The location, distribution, character and duration of the pain, together with the dyspnea, circulatory collapse, fever, leukocytosis, elevated sedimentation rate, pericardial friction rub, dilatation of the

heart, arrhythmias and electrocardiographic abnormalities, constitute a clinical picture that may appear indistinguishable from that of acute myocardial infarction. In order to make the correct diagnosis it is necessary to realize that the two conditions may resemble each other closely and then to consider certain of the features in detail. The differential diagnosis may be difficult. In 4 of the 5 cases described above a diagnosis of cardiac infarction was at first actually made or seriously considered, and in 3 of these 4 cases it was possible to discard the diagnosis of infarction only after careful observation. The following points have been found useful in differentiating acute pericarditis from acute myocardial infarction.

Pain. The distinguishing feature is accentuation of the pain by bodily movements, cough and inspiration. It is important to elicit the fact that characteristically the aggravation of the pain on exertion is not due to effort but to certain movements, such as turning over in bed. The aggravation of the pain by motion, cough and inspiration is present from the very outset in pericarditis, whereas when it occurs in myocardial infarction it is usually first noted twenty-four or forty-eight hours or more after the onset of the pain, and probably indicates that the infarct has extended to the pericardium or that some complication has arisen.

Dyspnea. Although dyspnea may be associated with pulmonary congestion, in most cases it can be ascertained that it is consequent to rapid, shallow breathing due to pain that interferes with the respiratory movements.

Pericardial friction rub. In most cases of myocardial infarction a friction rub is never heard; when present, it is rarely heard in the first twenty-four hours, is usually localized, and lasts only a short time. In acute pericarditis, on the other hand, the rub is heard within one to a few hours after the onset of pain, tends to be very loud, is audible over the entire precordial area, and is constantly present for days or for even one or two weeks.

Pleural involvement. Pleural involvement was demonstrated in 4 of the 5 cases of pericarditis by the presence of a pleural friction rub or by thickening of the pleura and a small collection of pleural fluid on x-ray examination. The fifth patient was not studied by x-ray.

Cardiac dilatation. The heart dilates in some cases of acute pericarditis[2] to a degree that exceeds that seen in myocardial infarction; nevertheless, myocardial failure does not occur in acute pericarditis. The only reliable method of detecting acute dilatation in these cases is teleroentgenography.

Abnormal ventricular pulsations. In 75 per cent of the cases of myocardial infarction a localized area of diminished, absent or reversed ventricular pulsations is found on careful fluoroscopic observation.[3-7] No such abnormalities of ventricular pulsation were demonstrable in these cases of pericarditis.

Electrocardiograms. Characteristic electrocardiographic patterns occur in acute pericarditis and acute myocardial infarction; they are readily differentiated in spite of certain similarities. The pattern in acute pericarditis is sufficiently distinctive to permit the diagnosis to be made even in the absence of a pericardial friction rub. Elevation of the RS-T segment is not accompanied by reciprocal depressions, the ascending limb of the T wave is straight or concave upward or the T wave is dome-shaped, significant QRS patterns do not occur, and the evolution of the entire pattern with reversion to normal takes place in a matter of weeks.[1] To avoid overlooking the pattern of infarction, however, an electrocardiogram should be obtained as early as possible, and be frequently repeated until the diagnosis is established beyond any doubt. Multiple chest leads should be used.

Fever. When temperature elevation occurs in pericarditis, it may be noted at the very onset of the attack. It may reach a higher level and last much longer than is usual in cases of acute myocardial infarction.

Pulse rate. The slowness of the heart rate may be striking in pericarditis; the average heart rate is slower than it is in cases of myocardial infarction.

White-cell count. Leukocytosis may be much greater and may last much longer in pericarditis than in infarction.

Age incidence. The ages of the above patients with pericarditis were thirty, twenty-nine, thirty-two, forty-one and sixty-eight years, respectively, a lower average than one would expect in myocardial infarction.

Manifestations of infection. Chilliness, chills, a "grippy" feeling and actual respiratory infection were more numerous in this series than they are in cases of infarction.

Discussion

The importance of not mistaking acute pericarditis for acute myocardial infarction needs little comment. The serious prognosis in the latter disease, the long period of incapacity and the frequent necessity of radically altering the patient's life contrast strikingly with the excellent prognosis and the expectancy of unrestricted activity in the former. In the one disorder there is always present the anxiety of some untoward event; in the other one can look into the future with confidence, even though recurrences of pericarditis occur in some cases.[2]

This problem in differential diagnosis has not been generally appreciated because of the belief that pericarditis usually or always occurs in association with rheumatic fever, tuberculosis, pneumonia, septic infections and cardiac infarction. The evidence warrants the assertion that in the cases here reported rheumatic fever, tuberculosis, septic infection and myocardial infarction can be excluded as etiologic factors. In Case 1 pericarditis complicated recovery

from primary atypical pneumonia; in Cases 2 and 3 it appeared without any previous illness or symptoms of infection, although pharyngeal injection was found in Case 2, and in Case 5 it occurred in an elderly man with chronic bronchial asthma. An unusual aspect in Case 4 was the coincidental presence of angina pectoris.

It is probable that the pericarditis in the cases here described was infectious in origin, although not of uniform etiology. With the onset of pericarditis in Case 4, manifestations of infection — that is, a "grippy" feeling, chill, a high white-cell count and marked febrile reaction — were prominent. Four or five attacks of pericarditis occurred during a seven-month period, illustrating, as did Case 2, the predisposition to recurrences. A benign, nonsuppurative, inflammatory pericarditis may apparently occur under various circumstances, unassociated with the commonly recognized causative factors. It may follow tonsillectomy. It has been reported following operative procedures[8,9] and has been observed in epidemic form.[10] Occurring as a postoperative complication and associated with a grayish pallor, a rapid, weak pulse and a drop in blood pressure, it may be erroneously diagnosed as pulmonary embolism or myocardial infarction.[9]

Barnes and Burchell[1] express the opinion that the correct diagnosis depends chiefly on the correct interpretation of the electrocardiographic changes, which they describe in detail. They do, however, consider the age incidence, the relation of the pain to inspiration and the marked cardiac dilatation as helpful in making the correct diagnosis. These, as well as the other manifestations discussed above, should establish the diagnosis on a firm basis.

Summary

Five cases of acute nonsuppurative pericarditis are reported in which the clinical picture strikingly simulated that of acute myocardial infarction. The latter diagnosis was at first erroneously made in 4 of them.

It is important to make the correct diagnosis, since in pericarditis prolonged and careful treatment is not necessary and the prognosis is excellent, in contrast with the seriousness of myocardial infarction.

The differential diagnosis is discussed and shown to be based on meticulous consideration of clinical, laboratory, electrocardiographic, teleroentgenographic and fluoroscopic data.

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MEDICAL PROGRESS

DIABETES MELLITUS

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Alloxan Diabetes

THERE are now three methods by which diabetes can be caused experimentally: the removal of the pancreas, discovered by von Mering and Minkowski; repeated injections of anterior pituitary extract, finally accomplished by Young but based on the work of Houssay, Evans and others; and the injection of a chemical — namely, alloxan. In the April 17, 1943, issue of the *Lancet*, Dunn, Sheehan and McLetchie[1] in Glasgow described how they had produced a selective necrosis of the islands of Langerhans of the pancreas in rabbits by injection with alloxan. Within a few weeks this paper was followed by others from groups from Chicago, Boston and Glasgow, in which it was shown, as might be expected, that if the animals were kept alive, diabetes developed as a result of the necrosis of the islet tissue.

Chemically alloxan is the ureide of mesoxalic acid, and as a result of its four carbonyl groups it is chemically a very active substance. Structurally it is closely related to the purines, particularly to uric acid. It may act either as a strong reducing agent or as an oxidizing agent. Its activity as an oxidizing agent is probably directly related to its ability to act as a hydrogen acceptor. As a hydrogen acceptor its affinity for the sulfhydryl groups may be of particular biologic significance.[2] Lehmann[3] found that alloxan inhibits the conversion of the Cori ester to the Robison ester and in higher concentrations the formation of the Cori ester itself.

Alloxan is readily soluble in water, forming a slightly acid solution. It is relatively stable only in acid solution. Labes and Freisburger[4] suggest that the mild alkalinity of the blood and tissues is probably sufficient to cause decomposition of any free alloxan almost immediately unless it enters into some other reaction. Through reduction it becomes alloxantin, whereas through oxidation it changes to parabanic acid.

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Alloxan is easily obtained from the oxidation of uric acid with nitric acid. Its relation to the role of uric acid in the body is, therefore, of possible significance. Uric acid in the human body originates exogenously in nucleoprotein in the food and therefore varies in amount according to the diet, but also originates endogenously. Uric acid eliminated in human urine amounts to 0.4 to 1.0 gm. daily, as compared with 20 to 35 gm. of the more highly oxidized urea. The excretion of uric acid is known to increase with muscle exercise. Muscle is not only the greatest consumer of sugar but is also the chief source of endogenous uric acid.

The deep significance of the production of diabetes by a chemical lies first in the simplicity and sureness of the method. Previous methods required technical skill or considerable time and labor. Furthermore, by pancreatectomy or by injections of mixed anterior pituitary extracts, other tissues than the insulin-producing islands were involved. Moreover, the use of the rabbit and rat affords animals easily available and suitable for research, thus opening up avenues for investigation of diabetes that were previously unavailable. The importance of the discovery merits a more detailed summary of these studies.*

In 1937, Jacobs[4] found that alloxan produced fatal hypoglycemia when injected intravenously into rabbits. Microscopic studies of the pancreas were not made. Recently in studies on the crush syndrome and mismatched blood transfusions Dunn experimented with injections of uric acid, which he had previously observed caused a selective lesion in the distal convoluted tubules and collecting tubules and other allied substances. He noted that alloxan gave promising results but that the animals died within the first day or so with symptoms not referable to renal disease, and it was in the course of these investigations that a lesion was found in the islands of Langerhans.

In a protocol of one of the rabbits three doses of alloxan were given intravenously in half an hour, each dose amounting to 100 mg. per kilogram of body weight in a 2 per cent solution of distilled water. The next morning the rabbit was in a feeble state, and later it was comatose, with slow, feeble breathing. The rectal temperature, normally 102 to 103°F., was below 93°F. The animal was chloroformed and an autopsy performed twenty-eight hours after the beginning of the experiment; the blood urea was 101 mg. per 100 cc., but the blood sugar was only 59 mg. compared with a normal of 100 to 140 mg. The kidneys showed an early tubular nephritis. No changes in other organs were noted save in the pancreas. Dunn, Sheehan and McLetchie describe these as follows:

> The acinar tissue appeared normal; some eosinophil casts were present in ducts. The islets of Langerhans were all abnormal; in most of them there was complete necrosis of the central cells, leaving only a ring or a crescent of live cells at the periphery; rarely, all the endocrine cells were necrotic. The protoplasm of the dead cells had the characteristic appearance of coagulative necrosis and often their bodies had fused into a mass. The nuclei had lost all the normal basophil staining of chromatin and took on eosin more intensely than did the protoplasm; their edges were ill defined as if they were undergoing lysis. The surviving peripheral cells generally had nuclei of normal appearance, as had sometimes their protoplasm, but very often the cell bodies were somewhat swollen and definitely eosinophilic though evidently not necrosed; in some of these the nuclei were small and hyperchromatic.

In subsequent experiments death occurred in twelve to twenty-eight hours following the injection, save in one rabbit that was killed in forty-eight hours and another that was killed on the fifth day. All the rabbits injected with alloxan showed some degree of islet necrosis. The authors concluded that a single intravenous dose of 300 mg. per kilogram of body weight given to an adult rabbit of average nutrition could be depended on to produce an extensive lesion of the islands, with characteristic symptoms. The blood sugar, initially 100 to 140 mg. per 100 cc., rose considerably for the first one or two hours, reaching 380 mg. in one case, and then fell in three to five hours to 100, 50 or even 30 mg. The terminal phase may not always have been seen, the animal having been killed to ascertain the state of the pancreas. No glycosuria was detected in any of these animals.

These authors summarize their work in part as follows:

> Acute necrosis of almost all the islet tissue of the pancreas has been observed in rabbits after intraperitoneal inoculation of a synthetic styryl-quinoline, and also after intravenous inoculation of alloxan. The development of this lesion is accompanied by an initial rise of blood sugar, followed by an intense hypoglycemia which ends fatally with subnormal temperature in twelve to eighteen hours. It is suggested that the lesion may be caused by overstimulation of the islets with overproduction of insulin, and later death of the cells from overstrain. The mechanism of production of the lesion is discussed and reference is made to the possible role of alloxan as a hormone of muscle.

* * *

In a letter to the editor of the *Journal of the American Medical Association*, Brunschwig, Allen, Goldner and Gomori[5] confirmed the work of the Glasgow observers and also stated that they had observed animals that survived injections of alloxan and exhibited only transitory hyperglycemia. They found that alloxan in doses of 200 to 500 mg. per kilogram of body weight was fatal to dogs in one hour to five days. They also noted that the transitory hyperglycemia was followed by hypoglycemia and by the end of forty-eight hours a pronounced hyperglycemia again occurred, which persisted in five dogs for two or three weeks. They also injected alloxan into 3 patients with carcinomatosis, apparently without much effect. In a subsequent communication, however, these cases and 2 others, in one of which the patient had an insulin-producing pancreatic carcinoma, were studied in detail by Brunschwig, Allen, Owens and Thornton,[6] who confirmed the earlier work in showing little influence of alloxan on the first 3 cases of noninsulin-producing cancer.

*Brief mention should be made of another chemical, styryl-quinoline No. 90, of which the full name is 2 (*p*-acetylamino-styryl) 6-dimethyl-amino-quinoline methochloride. According to Dunn, Sheehan and McLetchie, this substance, prepared by Cohen and Ellingworth, when tested by Browning and Gulbransen was found to have curative properties for infections with *Trypanosoma brucei*, but was inapplicable because it sometimes caused acute nephritis. In a subsequent study of this nephritis in rabbits, Sheehan observed that the animals lay prone with the hind legs stretched and the head tilted upward, with rapid respirations. The blood examination revealed a rise of blood sugar as high as 500 mg. per 100 cc. and the animals died in twelve to eighteen hours. Histologic examination showed a necrosis of the islands of Langerhans. No distinctive lesions were found in any other organs save the kidneys.

The alloxan did show a distinct reduction in the hypoglycemic attacks of the patient with the malignant tumor of the islet cells. The patient had had marked attacks, dating as far back as 1937, and had undergone operations for these by removal of islet-cell nodules from the pancreas or liver in September, 1939, in January, 1940, in August, 1942, and finally in December, 1943. Temporary symptomatic relief of these attacks was obtained, since the attacks were obliterated for a brief period following each series of injections. Shortly after the last laparotomy, the patient succumbed to an accidental complication. Autopsy revealed multiple metastatic nodules within the liver. Sections of the surgically removed pancreas showed normal acinar tissue and no evidence of necrotic islet cells. Sections of the tumor nodules showed viable tumor cells and no evidence of necrosis comparable with that seen in the islet cells in the pancreases of dogs and rabbits receiving alloxan. There was no evidence of acute damage to the liver cells, and no necrosis of the epithelium of the convoluted tubules.

Two other features of this case deserve mention. First, as a result of repeated attacks of hyperinsulinism, a tolerance for low blood-sugar levels had developed and the patient was able to conduct himself normally with a level as low as 20 mg. per 100 cc., the attack level being 14 mg. or less. Second, forced ingestion of food in an attempt to ward off hypoglycemic attacks resulted in a 35-pound gain in weight over a period of seven months after the carcinomatosis of the liver was proved by laparotomy, thus suggesting, as the authors state, that the cachexia of carcinoma is merely the result of a gradual reduction of the caloric intake and not of a toxemia originating from tumor cells.

The fifth patient was given the largest single injection of alloxan of the entire group, and died six hours after termination of the injection. This patient had a large carcinoma of the lower rectum, which had been previously excised. The patient returned with various complications, and reacted with few symptoms on August 27, 1943, when he was given 200 mg. of alloxan per kilogram of body weight, dissolved in 1000 cc. of an isotonic solution of sodium chloride. On September 1, however, when he received 600 mg. per kilogram of body weight, dissolved in 1200 cc. of saline solution, he developed a moderately severe chill and cyanosis and some six hours later, having apparently recovered from the symptoms following the injection of alloxan, suddenly died.

* * *

If alloxan produces extensive necrosis of the islands of Langerhans without damage to its acinar tissue and relatively minor changes in other organs, so argued Bailey and Bailey,[7] it would be reasonable to suspect that the hypoglycemic phase following the injection of the drug is transitory. Should this prove to be true, animals kept alive by repeated injections of dextrose might survive this hypoglycemic phase and finally develop diabetes mellitus. A series of experiments designed to test this hypothesis showed that such is the case.

Three-month-old male Dutch rabbits were employed. Each received intravenously 200 mg. of alloxan per kilogram of body weight, the injection being given in three parts over a period of forty-five minutes. The rabbits were observed continuously for sixteen to twenty-four hours, and 50 per cent glucose was given intravenously whenever hypoglycemic convulsions occurred. These authors also found an initial transitory hyperglycemia lasting approximately one hour after the injection of alloxan, followed by severe hypoglycemia with convulsions, but in less than twenty-four hours the hypoglycemic stage ended, leaving the animals with severe diabetes. Blood-sugar levels during the diabetic state ranged from 360 to 700 mg. per 100 cc. and glycosuria up to 10 per cent. One rabbit not given insulin developed acetonuria, total acetone bodies of 144 mg. per 100 cc. and pronounced lipemia, with total blood lipids of 8412 mg. per 100 cc. Insulin, 1½ to 8 units daily, was given to control the diabetes.

Two rabbits were killed, and it was found that the cells, both alpha and beta, of all the islands of Langerhans had completely disappeared. No polymorphonuclear infiltration was seen. The blood vessels of the islands were preserved and appeared entirely normal. Some of the pancreatic ducts were moderately distended and contained eosinophilic material. Their epithelium, as well as that of all the acini, showed no changes detectable on microscopic examination.

The following is a representative experiment in the series:

Rabbit 1, weighing 1520 gm., was entirely normal during a 7-day period of observation. Food was withheld for 18 hours, at the end of which time two micro blood-sugar determinations were 105 and 100 mg. per 100 cc. Three hundred and four milligrams of alloxan (200 mg. per kilogram of body weight) was then injected intravenously in three divided doses at 15-minute intervals. Fifteen minutes after the end of the last injection the blood sugar was 208 mg. per 100 cc. An hour later it was 105 mg., and 2½ hours after the end of the injection it was 38 mg. The first convulsion developed 10 minutes later. Prompt recovery followed the administration of 2 cc. of 50 per cent dextrose intravenously. In the next 13 hours eleven more hypoglycemic convulsions occurred, each relieved promptly by dextrose intravenously. On the morning after the injection of alloxan the blood sugar was 190 mg. per 100 cc. and rose to 640 mg. on the 3rd day. The rabbit was kept in good condition for sixteen days by the administration of 2 to 4 units of insulin daily. The amount of insulin required constantly increased, and the blood sugars varied from 200 to 540 mg. Persistent glycosuria accompanied the hyperglycemia, the daily dextrose excretion varying between 10 and 22 gm. Definite polydipsia and polyuria were observed, with the water intake ranging between 350 and 700 cc. and urinary excretion between 160 and 470 cc. daily. The body temperature was 104°F. before the experiment was begun and fell to 99°F. at the end of 11 hours, but subsequently returned to normal.

Repeated urinalyses failed to show albuminuria or any abnormal sediments. The blood nonprotein nitrogen varied from 36.3 to 65.0 mg. per 100 cc., whereas normal controls taken prior to the experiments ranged from 42.6 to 60.0 mg.

Bailey and Bailey consider that the initial blood sugar rise may be similar to a transitory hyperglycemia produced in rabbits by the injection of a number of substances and therefore not of great significance.

The cause of the prolonged yet limited period — twelve to twenty-four hours — of hypoglycemia that follows the injection of alloxan is at the present time debatable. Dunn, Sheehan and McLetchie[1] suggest that it may result from a primary stimulation of the islet cells. Another possible explanation is that necrosis of the islets releases a large amount of insulin.

* * *

In a second article, Dunn, Kirkpatrick, McLetchie and Telfer[8] point out that selective necrosis of the islands of Langerhans in the pancreas has rarely been described in human beings. They cite Pettavel,[9] who in 1912 and again in 1914 observed it in a case of hyperthyroidism associated with alimentary glycosuria. Fischer[10] in 1915 noted necrosis in a child of six and a half years with severe and rapidly fatal diabetes, and cites Heiberg[11] as considering this lesion to represent the commencing defect that is commonly noted in diabetes. Dunn et al. reaffirmed their previous findings of necrosis in the islands of Langerhans in rabbits injected with alloxan. The acinar tissue of the pancreas remained in all cases histologically normal, even at the edge of totally necrosed islets. They cite only negligible changes as having been observed in the adrenal, thymus, thyroid and pituitary glands. In the kidneys the changes were fairly extensive, with necrosis of the proximal and sometimes of the distal convoluted tubules. The renal lesions they considered as probably due to concentration of the toxic agent in the tubules during the process of excretion, but whether this was caused by alloxan or a degradation product of the same was unknown. At times renal changes were minimal when the islet lesion was fully developed.

Fatal doses of alloxan in rabbits usually varied between 200 and 300 mg. per kilogram of body weight, the injections sometimes being divided over periods of a half to six hours. Three hundred milligrams invariably caused necrosis of the islands, although some animals survived.

Styryl-quinoline No. 90 is the only other chemical known to cause islet necrosis. The authors tried the effect of oxalic acid, uranium, guanidine and uric acid, with no comparable lesions resulting. They also tried glucose in solutions as strong as 25 per cent.

Alloxan produced similar lesions in rats and mice. Permanent glycosuria and many features of the diabetic state were recognized in 5 of 8 albino rats injected. The glycosuria could be controlled by insulin.

Death of the islet cells is the chief factor following injection of alloxan. No island remains unscathed, and in some islands apparently no cells survive. Any living cells are at the periphery, where they may share the blood supply of acinar tissue.

* * *

Subsequently Dunn and McLetchie[12] recorded their investigation of alloxan diabetes in the rat. With doses of 300 to 400 mg. per kilogram of body weight some acute damage of the islands of Langerhans was produced, occasionally with necrosis in the renal tubules. Glycosuria was observed with almost all the symptoms of diabetes in certain of the rats, although 1 rat appeared to be recovering after two months. The glycosuria was controllable with insulin. In these rats the protoplasm of the islets was eosinophilic and hyaline, with pyknotic nuclei. In two islands there was a peripheral layer of large cells free from necrosis, which the authors thought were alpha cells, the beta cells being the cells chiefly affected. Mitoses were rare. They describe an acute effect of alloxan as follows:

> No. 11 died, cold and drowsy, at 48 hours; there was no glycosuria. The changes in the islets were as in No. 9 but more severe, with more necrotic debris and more cells of doubtful viability; while obviously live cells were fewer. There were, in addition, very pronounced lesions in the small ducts in this pancreas, comprising dilatation and accumulation of wax-like eosinophil masses with leucocyte infiltration in the walls and in the interstitial septa; this lesion could be interpreted as an early pancreatitis.

They also noted that the general appearance of the islands suggested reparative changes, but they saw "none of the more characteristic islet changes described in the human disease — sclerosis or hyalinisation of islets or hydropic changes in their cells."

* * *

An intraperitoneal injection of 200 mg. of alloxan per kilogram of body weight was found to be almost invariably effective in producing diabetes by Gomori and Goldner[13] when given to 40 rats. Of the 27 animals studied in detail, only 4 were resistant to alloxan. All the others showed hyperglycemia and glycosuria. Ketonuria was observed from the third day on and was present on subsequent days in all animals that had a blood sugar level above 300 mg. Some of the animals had a pink urine on the first day after the injection. In rats killed at the end of twenty hours, an overwhelming majority of the beta cells were greatly shrunken. In some cases the cell cords either had disintegrated into individual cells or had coalesced into an almost homogeneous debris. On the second day these changes were more accentuated, and the beta cells had started to lose the typical staining of their granules. On the fourth and fifth days only an occasional beta cell could be seen. At the same time, agranular cells of an unidentifiable type appeared in large numbers and filled the areas previously occupied by the necrotic beta cells. At the periphery, the alpha cells had proliferated considerably. By the fifth and sixth days the islets were entirely free from debris and with the routine hematoxylin-eosin stain looked practically normal.

Special stains, however, showed that they consisted of agranular and alpha cells only, beta cells being completely absent. No vacuolation of the islet cells was recognized at any stage. Mitoses were extremely rare, and the acinar parenchyma showed no change. The liver contained very little glycogen after the second day but was otherwise normal, except in 2 animals in which focal necroses were observed. The kidneys showed nothing of importance except that, from the fourth day on, deposition of glycogen in Henle's loops was quite frequently observed.

Five "hooded rats" were resistant to alloxan, possibly owing, as the authors suggest, to the exceptionally large amount of islet tissue that this strain possesses.

The histologic changes of the pancreas obtained by a single intraperitoneal injection appeared similar to those obtained by Dunn, Sheehan and McLetchie[1] with repeated subcutaneous injections of alloxan.

* * *

Goldner and Gomori[14] have extended their observations on alloxan diabetes in dogs. According to the dosage of alloxan administered varying changes occurred, and they divide their experiments into four groups.

Group 1. Alloxan, above 100 mg. per kilogram. Dogs receiving this dosage died within eight hours in sudden convulsive attacks. Microscopical examination showed no changes in the islands. Although in one animal the glycosuria fell to 48 mg., death was not attributed either to hypoglycemia or to kidney damage.

Group 2. Alloxan, 75 to 100 mg. per kilogram. These animals were hypoglycemic, then hyperglycemic, and presented what the experimenters considered to be a uremic syndrome. They died in four to seven days, gradually becoming drowsy and then semicomatose, without convulsions but developing oliguria and eventually anuria. The hyperglycemia in 1 case reached 800 mg. per 100 cc. There was also a steady rise in nonprotein nitrogen, attaining in 1 case 275 mg. per 100 cc. In only 1 case was albuminuria noted. No ketonuria was found. Microscopically the absence of granules in the beta cells was apparent, but the alpha cells were unchanged. There was no vacuolation in the cells of the islands or ducts. Extensive necrosis of the convoluted tubules was apparent, with glycogen in Henle's loops. The liver was normal.

Group 3. Alloxan, 50 to 75 mg. per kilogram. Dogs receiving this dosage developed diabetic symptoms and signs — polydipsia, polyuria, loss of weight, hyperglycemia and glycosuria. There was no ketonuria, albuminuria or increase in nonprotein nitrogen, but there was an increase in lipemia and the respiratory quotient fell to about 65. Pathological examination revealed small islands, no normal beta cells and no hydropic degeneration of the beta cells. There were no mitoses of the islet cells. Extreme vacuolation of the epithelium of all intralobular ducts occurred in the later stages of the disease. The kidneys were normal save for the presence of glycogen. There was fatty infiltration of the liver, with 31 per cent lipids, and the phosphatase reaction was increased.

Group 4. Alloxan, 25 mg. per kilogram. This dose was ineffective.

In summary, intravenous administration of alloxan to dogs in a single dose exceeding 100 mg. per kilogram of body weight caused death of the animals within a few hours. A dose of between 75 and 100 mg. produced a diabetic uremic syndrome of which the animals died within a week. A dose of 50 to 75 mg. produced typical diabetes without renal lesions, and these animals were kept alive for weeks. The main histologic features were a disappearance of beta cells from the islets, profound vacuolation of the epithelium of the pancreatic duct and fatty changes of the liver. Doses of 25 mg. were without effect.

* * *

In studies on the insulin tolerance, Dragstedt, Allen and Smith[15] observed that more insulin appeared to be required to establish the control of glycosuria in dogs with certain types of partial pancreatectomy than in totally depancreatized dogs. Likewise, in 2 dogs made diabetic by the intravenous injection of alloxan, the requirement of insulin was 32 and 36 units of regular insulin daily, which Goldner and Gomori consider somewhat greater than that for depancreatized animals at the same period.

* * *

In their second article, entitled "Alloxan Diabetes with Diabetic Complications," Bailey and Bailey[16] have advanced materially the knowledge of the action of alloxan in rabbits and rats and have shown clearly how closely the disease in the experimental animal approaches that in human subjects. They report that cataracts were found in all such rabbits within four to six weeks after the diabetes was induced. These were chiefly subcapsular and were more advanced in the posterior cortex, where they appeared earlier than in the anterior cortex of the lens. Like previous workers, these authors found the histologic changes in the animals to be confined to the islands of Langerhans, save for mild tubular degeneration of the kidneys and slight fatty metamorphosis of the liver.

A gradual onset of diabetes, thus more closely resembling the usual variety found in human beings, was obtained by the Baileys when alloxan in doses of 40 mg. per kilogram of body weight was given to rabbits in repeated intravenous injections. In 2 such rabbits after the seventh and the thirteenth injection, respectively, the blood sugars were over 200 mg. per 100 cc. and were accompanied by glycosuria, and the islet cells showed a variety of lesions, described as follows:

> Some cells, especially those at the periphery of the islets, appeared essentially normal. In other cells, the nuclei were well preserved, as was the ground substance of the cytoplasm, but the granules were not present. Numerous cells presented a clear-cut picture of hydropic degeneration, which has been shown to be a reversible change. Among the cells with hydropic degeneration, there were occasional cells with large clear vacuoles but with the nuclei staining in a homogeneous manner and without chromatic pattern; this appears to be an irreversible change because of the nuclear damage. Mitosis was seen in several islet cells but in no instance was there more than one mitosis in an islet. This complex picture of normal cells, slightly injured cells, cells with hydropic degeneration, irreversibly damaged cells and mitosis in a single islet is not clearly duplicated in any other form of experimental diabetes or in human patients. It seems best interpreted as a complex response to an injurious agent with some cells capable of survival if the agent is removed, while others are dead and are being replaced by mitotic division of surviving islet cells.

In 1 rabbit, after cessation of injections, the diabetes seemed to disappear, but careful studies over

a period of two and a half months disclosed its persistence. Twenty milligrams of alloxan per kilogram, even if repeated three times a week for seventy-one days, did not produce diabetes, but 40 mg. per kilogram did so if repeated.

Alloxan diabetes was most readily produced in rats by subcutaneous injection. In 2 rats diabetic cataracts developed after two or three months. Diabetic acidosis was rare, but did occur with typical symptoms. In one rat, recovery took place with the help of insulin, but in another, diabetic coma developed, along with extreme polydipsia, a dry tongue, Kussmaul respiration and drowsiness, which finally led to unconsciousness and death.

The rats that received the alloxan intraperitoneally or intravenously instead of subcutaneously showed extensive necrosis of the liver and severe lesions of the kidney, predominantly tubular in type. The rat that received alloxan subcutaneously and developed diabetic coma did not have liver necrosis. Thus it was concluded that the subcutaneous injection of alloxan in doses of 200 mg. per kilogram was a feasible method for producing diabetes in the rat.

* * *

Hughes, Ware and Young[17] found islet-cell changes within five minutes of the subcutaneous ingestion of alloxan into rats. The large islets were not only the first damaged but likewise showed the greatest injury. The initial hyperglycemia ending in hypoglycemia that follows the injection of alloxan was reproduced in rabbits by the injection of adrenalin and protamine zinc insulin equivalent to the amount of insulin known to be present in the pancreas of a normal rabbit — namely, 10 units per kilogram of body weight. A valuable editorial in the same issue of the *Lancet*[18] recalls that Liebig, Lang and others claimed that alloxan could be found in animal secretions and that if alloxan is a constituent of mucoproteins its physiologic significance may be much greater than was ever thought.

Incidence of Diabetes

Blotner, Hyde and Kingsley[19] report studies in diabetes mellitus and transient glycosuria in 45,650 consecutive selectees and volunteers, aged from eighteen to forty-five years, in the Boston Armed Forces Induction Station. The incidence of diabetes that they found is approximately three to four times that of a nearly similar age group in 1935-1936, ascertained through a house-to-house canvass by the United States Public Health Service. This recent investigation of the incidence of diabetes deserves most careful attention, because the diagnostic methods were sound. Not only was the urine examined, but if sugar was found it was tested before and after lunch on the same day. If the urine repeatedly showed sugar and there was not a verified history of diabetes, the men were sent to an Army hospital for a 100-gm. glucose-tolerance test carried out after the subjects had fasted all night. Diabetes was diagnosed when the blood-sugar concentration reached a level of 180 mg. per 100 cc., and some or all of the specimens of urine contained varying amounts of sugar. The cases of mild diabetes usually showed normal fasting blood-sugar levels, rising to 200 or 220 mg. per 100 cc. and then falling in two hours to 150 mg. and in three hours to 100 to 125 mg.; those moderately severe presented a fasting level above 140 mg. per 100 cc., with or without glycosuria in the fasting specimen, but the blood sugar reached 275 mg. per 100 cc. and dropped to about 200 mg. in three hours. The severe cases showed a fasting level of about 275 mg., with considerable amounts of sugar in the urine; after the ingestion of glucose the blood sugar rose to about 475 mg. in one hour and dropped only slightly in three hours.

Transient glycosuria was diagnosed in the men who had varying amounts of sugar in the first specimen of urine tested but negative reactions on subsequent days. If, as the writers say, sugar-tolerance tests had been done on all these cases, it is probable that a number of additional cases of diabetes mellitus would have been discovered.

The cases of diabetes mellitus numbered 208, those of transient glycosuria 126, and those of renal glycosuria, as interpreted by the authors, 33.

The average age of the diabetic patients was 34.4 years and of the men with transient glycosuria 27.5 years. The control group averaged 27.5 years. The diabetic patients were on the average (158 pounds) about 18 pounds above the weights of 1000 consecutive selectees (140 pounds) and were of normal average height. Tuberculosis occurred in about the same proportion of the diabetic patients as of the nondiabetic subjects. A diabetic heredity was about six times as frequent in the diabetic patients — 32 per cent — as in the nondiabetic subjects used for control — 5.2 per cent. No significant variation was noted in the prevalence of diabetes in selectees from communities of different socioeconomic levels or in the prevalence in areas classified by welfare relief paid per capita. The incidence in dense urban areas was 0.8 per cent, as contrasted with 0.4 per cent in the least populated area, and this the writers attribute to the greater proportion of Jews and Irish in the former. Occupation proved to be of little significance. There were twice as many Jews in the diabetic group as in the control group, and nearly half again as many Irish in the diabetic group as in the control group.

I attach great importance to these studies. I have always believed diabetes to be commoner than statistics have revealed. To a slight degree I can confirm the accuracy of diagnosis as performed at various Army hospitals, because many men rejected by the Army, and by the Navy, as well, have later been seen by me for diagnosis and treatment. Of all those re-examined, a difference in diagnosis has probably

not occurred in more than 5 cases. The outstanding patient was one who was ill with a respiratory infection when he took the induction test and was rated a diabetic patient, but later when re-examined he was accepted. The other cases were apparently borderline ones, with the blood sugar varying between just above and just below the diagnostic level. The usual Army diagnosis was overwhelmingly correct.

Subsequent and similar studies may well change the entire conception of the incidence of diabetes in the United States, so far reaching are the implications arising from the studies of Blotner, Hyde and Kingsley.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor**
BENJAMIN CASTLEMAN, M.D., *Acting Editor*
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CASE 30141

PRESENTATION OF CASE

First admission. A forty-two-year-old yardman entered the hospital because of upper abdominal pain.

The patient had been in excellent health until six months before admission, when he noted episodes of indigestion, especially after meals; they were relieved by soda. These increased in frequency and severity, and about six weeks before entry he developed attacks of pain in the "pit of the stomach." Two weeks later he began to vomit four or five times daily, without any definite relation to meals. The pain increased in severity and became almost continuous. He lost 20 pounds in weight in about one month.

Physical examination showed a well-developed, somewhat emaciated man. The heart and lungs were normal. There was slight tenderness over an orange-sized mass situated in the left upper quadrant.

*On leave of absence.

The blood pressure was 108 systolic, 95 diastolic. The temperature, pulse and respirations were normal.

Examination of the blood showed a red-cell count of 4,700,000, with 90 per cent hemoglobin. The white-cell count was 7000. The urine was negative. A blood Hinton test was negative. A gastrointestinal series showed the entire stomach to be rigid. There was marked thickening of the wall. The mucosal pattern was absent.

Abdominal exploration on the seventh day showed a large carcinoma of the stomach with some small hard nodules in the gastrocolic ligament. The stomach was not fixed. The spleen was twice the normal size. A total gastrectomy with esophagojejunostomy and splenectomy was performed. A portion of the transverse colon was removed, and the middle colic vessels were sacrificed. It was impossible to close the defect in the mesocolon. Through a McBurney incision a complementary cecostomy was then performed. The pathological diagnosis was scirrhous carcinoma with metastases to the regional and celiac lymph nodes.

The patient withstood the operation well and had an essentially uneventful postoperative course. The cecostomy tube was removed and he was discharged on the twentieth postoperative day.

Second admission (six days later). Following discharge the patient did well except for occasional gas pains. About noon on the day of admission he developed an increasingly severe lower abdominal pain. The pain was steady in character and spread to the upper abdomen and down the left side. Five hours later, following a light supper, the pain became almost unbearable. There was no vomiting and only slight nausea. The stools, which had been

normal, were said to have become extremely hard and painful on that day. He had no chills, fever or sweats.

Physical examination showed a slightly distended abdomen. There was generalized voluntary spasm, maximal in the left upper quadrant. No masses were palpable. Peristalsis was normal in pitch but active. Rectal examination was negative.

The temperature was 99.2°F., the pulse 92, and the respirations 20.

Examination of the blood showed a white-cell count of 14,700.

X-ray films of the abdomen showed no free air under the diaphragm. The right half of the diaphragm was slightly elevated. There was an air-filled loop of small bowel in the left upper quadrant that showed a fluid level on standing and was apparently somewhat dilated. No other dilated loops were present. There were scattered areas of gas throughout the abdomen: moderate amounts in the large intestine, and possibly some in the small. The appearance of the abdomen was suggestive of fluid.

The patient was given 500 cc. of blood, as well as plasma and intravenous fluids. A Miller–Abbott tube was passed. Exploratory laparotomy under spinal anesthesia showed a moderate amount of dusky fluid and many white carcinomatous nodules. There were no dilated loops of bowel, no evidence of obstruction, and no leakage around the anastomoses.

Postoperatively the temperature ranged between 99.6 and 100.5°F. The abdominal distention increased. There was no audible peristalsis. The patient complained of pain in the testes and penis. There was considerable vomiting, and occasional hiccoughs. He was given additional intravenous fluids and transfusions. On the third postoperative day he developed jaundice. On the evening of the fifth postoperative day he suddenly went into shock, with profuse sweating and dyspnea. The blood pressure was unobtainable. He was quite distended, and peristalsis could not be heard. He died ten hours later.

Differential Diagnosis

Dr. Francis D. Moore: Just before the second operation x-ray films were taken. May we see them now?

Dr. Laurence L. Robbins: In this film, taken in the upright position, there are fluid levels and slightly dilated loops of small bowel. The descending colon is visible down to the sigmoid. These loops of small bowel are where the stomach and spleen used to be.

Dr. Moore: Usually in these conferences one is given a history and a physical examination; the patient goes to operation, and one tries to determine the diagnosis. Here we have a patient with two histories, two physical examinations and two operations, and still we do not know the diagnosis.

Everybody will agree that the fundamental lesion was scirrhous carcinoma of the stomach, and there is no use in spending more time on it. The problem is, What was the nature of the postoperative complication that was fatal?

As we go back over the history we find that at the first operation it was impossible to close the defect in the mesocolon. The esophagus was anastomosed to the jejunum. The duodenum was turned in almost unquestionably, and an enteroenterostomy done — it is not mentioned, but it is virtually routine in this type of anastomosis. The mesocolon coming across in front of the duodenum was brought around anteriorly and the transverse colon had to be cut as part of the operation, a portion being resected, including the middle colic vessels. So the patient had another suture line there. He also had a cecostomy.

As to the defect that was not closed — I think that is more or less of a red herring. Following a total gastrectomy, when the jejunum is brought up, it is unusual to be able to close the transverse mesocolon. If one did close it around two loops of small bowel, one might get into trouble from the closure because it would tend to cicatrize around the bowel. I should like to know what Dr. Sweet has to say about that. In my experience it is extremely unusual to close the mesotransverse colon in this procedure. Whether that is significant or not, I do not know, although there are factors later that suggest that something was going on at the root of the mesentery.

The patient was discharged on the twentieth postoperative day. With such an extensive operation, that must mean he had an extremely uneventful convalescence. He went home and for six days had occasional "gas pains." If we interpret these pains to mean the smooth-muscle peristaltic cramps of small bowel trying to put a fecal stream through or around an obstruction, we must admit that there was something wrong. This is infrequent with a gastrectomy of any sort, because the bowel distal to the esophagojejunostomy is not tampered with. It is out of the field of operation, and to have symptoms of small-bowel obstruction lower down is unusual.

On the day of the second admission the patient developed severe pain in the lower abdomen, which spread upward and down the left side. Possibly one should lay stress on the fact that it started below the umbilicus; but it apparently became diffuse and fits in with the concept that he was having smooth-muscle pain in the small bowel. Five hours later he ate supper, after which he became much sicker, which suggests that the obstruction, if he had one, was high up so that eating a meal immediately filled the obstructed loop. When he was admitted he had a slightly distended abdomen and mild spasm, which are compatible with obstruction.

There was no free air, which is comforting. At least there was no perforation.

Then we come to the x-ray examination, which showed air in the large bowel. One might argue that that is evidence against small-bowel obstruction, but it is worth pointing out that with early, high small-bowel obstruction a patient may maintain gas and feces in the large bowel for twenty-four hours before he expels them. Thus, in the first twelve, eighteen or twenty-four hours of high small-bowel obstruction it is possible to find dilated loops as well as gas and feces in the large bowel. Whether the loops in that x-ray film are dilated is open to argument. The haustral markings are coarse, which is characteristic of jejunum rather than of ileum. The finding, however, of frank fluid levels in this area in the vertical position strongly suggests that they are pathologic.

A Miller–Abbott tube was passed. That is interesting because a Miller–Abbott tube could have gone two places in this man: down the esophagus and into the afferent loop or down the esophagus and into the efferent loop, depending totally on the mechanism of the anastomosis. The chances are that it went into the efferent loop, and I think that that is important.

Exploratory laparotomy under spinal anesthesia then showed dusky fluid and white carcinomatous nodules. That is discouraging but probably did not have a great deal to do with what killed him. The dusky fluid in the face of an otherwise negative laparotomy is still compatible with my working diagnosis, because one of the first things that happens in the peritoneal cavity in small-bowel obstruction is the transudation of fluid, and a dusky brown color is characteristic. When they operated on this man, if he had been obstructed, his obstruction had been reduced, or if he had had an internal hernia, it had been reduced, and all they found were the leftovers of the obstruction — nothing that they could remedy. There is no comment on where the Miller–Abbott tube was or how far it went down, but since the patient had no pylorus I assume that it went down a foot or two into the upper jejunum.

Dr. Gordon A. Donaldson: We did not follow it.

Dr. Moore: I think that the findings at operation were compatible with reduced small-bowel obstruction. There was no leakage around the anastomosis. The fact that there was no audible peristalsis postoperatively is of no significance because of the short period of time postoperatively. One would not expect normal peristalsis to get going so soon.

The pain in the testes and penis is hard to interpret, but the lymph, blood and nerve supplies of the testis originate in the somatome that is associated with the kidney. The spermatic arteries come from there, and so it is conceivable that something was going on at the root of the mesentery: tumor, lymphadenitis, torsion or decreased blood supply.

There was considerable vomiting. That is certainly an unusual thing in a person with no stomach in whom a Miller–Abbott tube had been passed. One would not expect vomiting. In the first place it is difficult to visualize because fluid has to run back up from the anastomosis in order for the patient to vomit. That is evidence that there might have been obstruction of a loop into which the Miller–Abbott tube had not passed. This could have been the afferent loop or the loop running from the duodenal closure to the anastomosis.

On the third day the patient developed jaundice. That is an interesting finding. Of course it could have been due to a lot of factors. He could have had carcinoma in the liver sufficiently extensive to give jaundice, or carcinoma around the extrahepatic biliary tree giving obstructive jaundice. But, on the other hand, he became jaundiced with the acute episode and I think it is fair to assume that all of it was part of the same process. Where could he have obstructed a loop of bowel that would produce jaundice? The answer is, The afferent loop. If this loop was obstructed, it is tantamount to obstruction of the common duct, which comes down and enters the afferent loop at the papilla. If that was obstructed, he could not drain bile, would get retrograde pressure back through the papilla and might get jaundice.

On the fifth day he went into shock, with profuse sweating and dyspnea. There are two things that could produce death that rapidly in this man. One is massive intraperitoneal hemorrhage or, as a matter of fact, hemorrhage anywhere. I say "intraperitoneal" because he did not bleed externally. Did he have that? He could have had it, but I do not believe that that is what he had. I think that something perforated and that he died of the shock of a tremendously overwhelming chemical peritonitis. The perforation of a suture line in a portion of bowel that is obstructed below is a much more dramatic and much more shock-producing event than any other form of perforated viscus of which I know. A perforated peptic ulcer classically is supposed to produce shock. Yet of the patients that come to this hospital for perforated peptic ulcer only a very few are in shock. But a patient who is obstructed, "blows out" a suture line and floods his peritoneal cavity with a tremendous amount of intestinal contents, goes into shock and dies rapidly if there is nothing to wall it off.

Can a loop of bowel become obstructed and perforate in this short period of time? It was five days at the most, since we know that the patient did not have obstruction at the second operation. If there were nothing in the bowel to weaken it, such as a suture line or a tumor, I think that the answer is, No. A loop of small bowel may be strangulated for some time before it perforates, and during that period it usually becomes adherent to adjacent loops and may never have free peritoneal perforation.

So that fits in with the general concept that there was obstruction of the afferent loop, which had not been drained by the Miller–Abbott tube, had been reduced at the first operation, had become re-obstructed, had produced jaundice and had eventually blown out one of the three suture lines.

What are the other possibilities? Massive hemorrhage? I do not believe so. Could he have perforated or blown out the suture line in the transverse colon? Yes, but I do not believe that he did. Did he have a completely separate and independent lesion — another carcinoma — that obstructed? Possibly, but there is no evidence for it. Someone may say that thirty-one days after the first operation is too long to have blown out a suture line. It is true that the usual time is seven to ten days, but this man did not have a suture line alone — he had a suture line plus obstruction below it, and the suture line gave out simply because it was the weakest point in the system. Why did he have obstruction of the proximal loop? There are two possibilities. One is that the bowel became kinked at one of the two anastomoses. The other, which is the more likely, is that the patient had a long afferent loop that became herniated into the left upper quadrant behind the efferent loop. That is my diagnosis. He had an obstructed afferent loop — possibly a hernia into the left upper quadrant — that had been reduced at the time of the second operation, became obstructed again and finally blew out the duodenal suture line.

Dr. Richard H. Sweet: I should like to suggest that the lethal episode that this man suffered was the result of acute pancreatitis. Furthermore, at the second operation it is possible that he might have had an unrecognized pancreatitis.

The other point that I should like to raise is that if Dr. Arthur W. Allen operated on this patient it is unlikely that the patient had a long proximal loop, since that is contrary to his technical method in this type of operation.

Dr. Moore: If the patient had a short proximal loop it would be unlikely that he had a hernia of it. He could, however, obstruct the afferent loop by a kink at the anastomosis.

Dr. Sweet: Dr. Allen told me once that he made a great point of placing the enteroenterostomy in this operation as close as possible to the ligament of Treitz.

Dr. Moore: Do you agree that the closure of the mesocolon is unusual?

Dr. Sweet: It is in my own practice. I never do it after total gastrectomy.

Dr. Moore: It was possibly a herniation of small bowel independent of the anastomosis, through the rent in the mesocolon; and yet I do not think that is what he had because, as Dr. Sweet has pointed out, it is unusual to close such a rent.

Dr. Sweet: I should like to qualify my statement, because this is not strictly a surgical audience. We do close the rent in the mesocolon in subtotal gastrectomies, but we do not do it in total gastrectomies. Closure of the mesocolon around the loop of jejunum is carried out by some surgeons, I am sure; but my own feeling is that it is better not to, or at least that it is unnecessary.

Dr. Chester M. Jones: I should like to raise a question about jaundice caused by obstruction in the proximal jejunum or end of the duodenal loop. It must be an unusual occurrence.

Dr. Moore: I saw one patient without biliary tract disease but with an obstructed afferent loop after a subtotal gastrectomy who developed jaundice of a minor order. How much jaundice was there in this patient?

Dr. Benjamin Castleman: It was reported as mild on the ward, but it must have gradually increased because at autopsy there was significant jaundice.

Dr. Moore: He could have had biliary tract disease entirely independent of the acute episode — biliary tract disease with obstruction of the duct and perforation of the gall bladder.

Dr. Castleman: Will you elaborate on the second operation, Dr. Donaldson?

Dr. Donaldson: We were reluctant to operate and waited about twelve hours. This we would not have done if the patient had not had the operation four weeks previously and undoubtedly presented a good many adhesions. Moreover, an x-ray film was taken, which apparently was not reported: a swallow of barium after the first operation showed air-filled loops of bowel in the left upper quadrant. Another reason why we delayed was that the type of pain was unusual. It was lower abdominal pain.

After waiting for twelve hours, however, with a rise in the white-cell count and increased tenderness, we thought that we had to do an exploration and were quite disturbed to find a small bowel that showed no evidence of obstruction. We were able to put a hand behind the mesocolon and feel the proximal and distal loops, which were not dilated. He did have diffuse carcinomatosis.

Dr. Moore: Did you feel the gall bladder?

Dr. Donaldson: The right upper quadrant was filled with loops of adherent jejunum.

Clinical Diagnoses

Scirrhous carcinoma of stomach, with metastases to regional lymph nodes and peritoneum.
Operations: total gastrectomy and splenectomy.
Pulmonary embolus?
Acute generalized peritonitis?

Dr. Moore's Diagnoses

Scirrhous carcinoma of stomach, with metastases to regional lymph nodes and peritoneum.
Operations: total gastrectomy and splenectomy.
Small-bowel obstruction.
Rupture of duodenal suture line.
Acute generalized peritonitis.

Anatomical Diagnoses

(Scirrhous carcinoma of stomach with metastases to regional lymph nodes.)

Carcinomatous metastases to peritoneum.

Operations: total gastrectomy and splenectomy.

Thrombosis of splenic, portal and superior mesenteric veins.

Mesenteric venous thrombosis, recent.

Infarction of small intestine.

Pathological Discussion

Dr. Castleman: The autopsy on this man showed, in addition to a moderately infected abdomen, a loop of small bowel about 100 cm. long that had all the characteristics of infarction and early gangrene. This loop was somewhat bound down and when dissected was located about 100 cm. from the ligament of Treitz. Examination of the mesentery of that loop showed that all the veins were filled with recent thrombi, probably three or four days old. Certainly this loop of bowel was not involved at the time of exploration or it would have been observed. The splenic vein was also completely thrombosed, but this was an old thrombosis — apparently resulting from splenectomy at the time of the first operation. The splenic-vein thrombus extended for a short distance into both the portal and superior mesenteric veins. Within the liver many of the radicles of the portal vein were likewise occluded by thrombi of all ages, which probably accounted for the jaundice. It is possible that during the second operation, in manipulating to try to find the area of obstruction, a small thrombus was broken off, which entered the vein returning blood from the involved loops and caused retrograde thrombosis. Of course, that would have been against the flow of blood, but such a stream may be sluggish, especially in the presence of peritoneal irritation from metastases and infection.

We have seen two other cases in which, following splenectomy associated with a gastrectomy, small thrombi were found in the portal radicles of the liver and in the splenic vein. Perhaps that occurs oftener than we suppose, and the patient gets away with it. In one of these cases the patient died of peritonitis following a rupture of the anastomosis. Perhaps removing the spleen along with a gastrectomy is not without danger. Have you any comment, Dr. Sweet?

Dr. Sweet: I have recently given that a lot of thought. I wonder if the thrombosis in the tied-off splenic vein may not be the cause of the so-called "postsplenectomy fever," which often follows splenectomies, especially those performed in cases of Banti's syndrome, whatever that may be. This is a long-lasting fever, which gradually subsides after a period of weeks.

Dr. Castleman: The patient had fever following the first operation but it soon disappeared.

Dr. Sweet: This is not at all clear. You have not proved to my satisfaction that the bowel lesion that you discovered existed before Dr. Donaldson's operation, or that it caused pain in the lower abdomen.

Dr. Castleman: Perhaps not at that operation; the gangrene of the bowel was a recent event.

Dr. Sweet: Probably following Dr. Donaldson's operation. What was the cause of the symptoms before?

Dr. Castleman: Probably the thrombosis of the splenic vein.

Dr. Sweet: Then I should like to ask Dr. Jones if pain from such a thrombosis would be referred to the lower abdomen. I doubt it.

Dr. Jones: This patient's pain sounds much more like that of a pancreatitis. I should agree with Dr. Sweet that pain arising from a splenic-vein thrombosis presumably would be high in the abdomen or in the back, or in both.

Dr. Donaldson: It started in the lower abdomen but soon spread to the left upper abdomen.

Dr. Jones: Did he have enough carcinomatosis to produce pain?

Dr. Castleman: No.

Dr. Sweet: The localization of pain is so important in the making of a diagnosis that in cases of this sort we ought to have it clearly in mind that it often occurs in the upper abdomen.

Dr. Castleman: The final localization of the patient's pain in the left upper quadrant is consistent with thrombosis of the splenic vein.

CASE 30142

Presentation of Case

A twenty-seven-year-old Norwegian seaman entered the hospital because of increasing pain in the right hip.

The patient was in perfect health until about five years before admission, when he developed a painful right knee. He was seen by a physician, who told him that his hip was the involved joint. He was treated by bed rest, with great improvement. The pain apparently disappeared until two years before entry when, after being kicked in the thigh, he began to notice pain and limitation of motion in the right hip. He was hospitalized for eight months, after which he was able to return to work. Subsequently, however, the pain increased in severity and there was considerable limitation of movement. He walked with a limp. No other information was available.

Physical examination showed a well-developed and well-nourished man in no distress. The heart, lungs and abdomen were normal. Hip flexion on the right was limited by pain to 90°. Internal and external rotation was limited by pain to 15°. Flexion and extension of the hip produced a grinding motion

and palpable crepitus. There was no discernible atrophy or shortening of the limb.

The blood pressure was 125 systolic, 73 diastolic. The temperature, pulse and respirations were normal.

Examination of the blood showed a white-cell count of 6000, with 70 per cent neutrophils. The hemoglobin was 15.1 gm. per 100 cc. The urine was negative. The sedimentation rate was 12 mm. in sixty minutes. A blood Hinton test was negative.

X-ray examinations of the right hip showed a rounded area of diminished density in the acetabulum and along the superior side of the neck of

FIGURE 1. *Roentgenogram of Right Hip Joint.*

the right femur, with very little bone reaction (Fig. 1). The joint spaces were slightly narrowed, but the joint surfaces were intact. The head of the femur showed some flattening. In the lateral view the shaft displayed moderate atrophy and coarse trabeculation. X-ray films of the chest were negative except for adhesions to the left diaphragm.

On the third hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. JOHN REIDY: We might start by looking at the x-ray films.

DR. LAURENCE L. ROBBINS: These are the areas of rarefaction that were described, with the narrowing of the joint and the flattening of the head. It is quite impressive, particularly in comparison with the previous case,* to see the lack of bone reaction. The decalcification in the right side of the pelvis as well as in the femur is probably on the basis of atrophy. The chest is essentially negative.

DR. REIDY: The adhesions in the chest could have been the result of an infectious process. Is there any evidence of tuberculosis?

DR. ROBBINS: There is possibly some fibrosis in the upper lobes, particularly on the left, but even that is questionable. This could be attributed to old tuberculosis, and the adhesions could be on the basis of an old pleurisy. Certainly there is no evidence of active tuberculosis.

DR. REIDY: This man was relatively young, twenty-seven years old, with quite limited hip function and considerable pain that was sufficient to force him to stop work. He had been hospitalized on several occasions over a relatively long period, and the last time he had been immobile for a period of eight months before he was able to get about. On the first occasion we do not know how long he was kept in bed, but it was probably for a fairly long period.

On physical examination there was little other than limitation of motion, described as having been due mostly to pain, but probably also because of the deformity, since one factor rarely causes limitation of motion. It is unusual to see so much atrophy of the bone and none in the soft tissues of the extremities. The description in the physical examination says that he had no discernible atrophy of the thigh.

We have to rule out the possibility of an old slipped epiphysis, which I think is most unlikely since the hip was in relatively good position, although it could have slipped slightly, in that the anterior lip in this film is a little low. That could produce traumatic arthritis due to faulty mechanics of the hip joint.

Legg–Perthes's disease is a possibility, but more broadening of the head and flattening would be expected in that condition. The lesion in question shows narrowing of the joint space. In addition to the diminished density in the acetabulum there is also some evidence of destruction in the head of the femur, which could be the result of a disease process crossing the joint or just due to disuse. It could occur, however, as the result of trauma.

Gout is most unlikely. Nothing is said of an elevated blood uric acid, and the x-ray picture is, I believe, unlike it; although I have seen a case somewhat similar to this, in which a gouty node was removed from the capsule of the hip joint. A malignant neoplasm is also unlikely since, after five years, one would expect more destruction than we see here.

*Case records of the Massachusetts General Hospital (Case 30131). *New Eng. J. Med.* 230:409-412, 1944.

A low-grade inflammatory process, I believe, is the thing that must be considered. There is no help so far as blood count or sedimentation rate is concerned.

Osteochondritis dissecans, again the result of trauma, is a possibility, particularly in view of the fact that they mention a grinding sensation, which might mean that a portion of the acetabulum or head of the femur had been broken off into the hip joint, although the crepitus might well be accounted for by the irregularity and the defect in the acetabulum.

I believe that we should also consider xanthoma or Gaucher's disease. I have seen a case of Gaucher's disease with a lesion in the acetabulum similar to this that did not cross the joint and therefore had produced no change in the head of the femur.

In a young man of twenty-seven it is unusual to have a traumatic arthritis of this degree. I should think that he probably had a low-grade infection, since there is no evidence of anything acute, and a tuberculous lesion should be seriously considered. Tuberculosis of the acetabulum does occur but less frequently than does tuberculosis of the head. X-ray evidence of involvement of the head, with a moderate degree of atrophy and destruction, should permit us to consider tuberculosis as a thoroughly tenable diagnosis.

There is another unusual lesion that might be mentioned in this case, in view of the fact that he was a seaman. Had he done any diving?

Dr. Marius N. Smith-Petersen: In spite of the history, he was not a seaman.

Dr. Reidy: If he had been a diver, caisson disease might be considered. Sometimes the vessels in the terminal portions of the bone become occluded and an aseptic necrosis results, with a picture similar to this and destruction of the joint as the lesion goes on.

To summarize, this man had a fairly extensive lesion in the hip, considerable atrophy of the bone about the hip joint, a definite area of bone destruction in the acetabulum and another area of destruction in the head of the femur, with narrowing of the joint. The fact that he improved with long periods of rest, only to have recurrences, is suggestive of a low-grade infection, and I make tuberculosis my first diagnosis rather than a neoplastic type of lesion.

Dr. Smith-Petersen: One cannot afford to belittle the changes in the head and neck of the femur, because there was distinct change in the architecture of the two. The changes in the epiphyseal line are perfectly consistent with several epiphyseal slips. The patient had symptoms at the age of twenty-one. At that time he was beyond the stage of a slipped epiphysis, but in skiing he must have been exposed to trauma and could have had minor slips earlier in life to which he paid little attention. After twenty-one, he had symptoms perfectly consistent with faulty architecture and at that time was in bed for six or seven months.

Our preoperative diagnosis was traumatic arthritis secondary to faulty architecture, which would account for the changes in the acetabulum. Whether it began as cystic degenerative change, we did not know. At the time of operation, on approaching the joint, the anterior acetabulum was cut through and the cut went across those areas that you see, which contained pink gelatinous material. There was some discoloration of the adjacent articular cartilage. The changes in the head were perfectly similar to the changes that one finds in malum coxae senilis, in which there are cystic areas; but that is not what these areas represented. To call them cysts is hardly correct. They were degenerative fatty areas that when squeezed oozed material similar to olive oil. There was villus change in the inferior compartment but the villi were not the ordinary type. The joint did not have the appearance of a joint that was or had been infected, nor did it resemble tuberculosis in any way, shape or manner. The postoperative diagnosis was traumatic arthritis, and a cup arthroplasty was done.

Clinical Diagnosis

Traumatic arthritis.

Dr. Reidy's Diagnosis

Tuberculosis of acetabulum, head of femur and hip joint.

Anatomical Diagnosis

Tuberculosis of hip.

Pathological Discussion

Dr. Benjamin Castleman: Microscopic examination of the synovial lining of the joint, as well as that of the bone of the head of the femur, showed tuberculosis.

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HOSPITALIZATION FOR ACUTE COMMUNICABLE DISEASES

There are many good reasons for reconsidering the role of special contagious-disease hospitals. In recent years a definite change in attitude toward certain diseases has occurred, and they have been taken out of the class of those that are considered suitable for isolation in special hospitals. An example of immediate interest is meningococcal meningitis. In the past, cases of this disease have been considered especially suitable for care in isolation hospitals but now they are being treated in the wards of general hospitals without difficulty. The problem of isolation and quarantine in cases of scarlet fever has been considered in a recent editorial in the *Journal*.[1] It is quite incongruous in the light of present-day understanding of streptococcal infections to consider scarlet fever as the only one of a group of hemolytic streptococcus diseases that requires isolation in special contagious-disease hospitals, while patients with tonsillitis or septic wound infections are treated in the open wards or in single rooms of general hospitals. Smallpox may be considered as an extreme example. But even with this disease the facts that vaccination against it is practically universal and that the immunity of the hospital personnel can be maintained by frequent revaccination make it perfectly feasible to treat cases of this disease in single rooms in general hospitals.

General hospitals are, willingly or otherwise, treating cases of all sorts of communicable diseases at the present time. Many patients are admitted before the correct diagnosis is made and when they are presumably at the height of their contagiousness, and when the possibility of communicable disease is entertained, the staff of the hospital must be prepared to use proper technic to avoid transfer of infection to themselves and to others. This makes it quite essential for the entire staff to be acquainted with the technics that limit the spread of contagious diseases.

The diagnosis and care of open cases of tuberculosis, although different in many respects from those of other acute communicable diseases, present some problems along the same line. The special hospitals for the care of such cases are overcrowded, and even when beds in such sanatoriums are available, many patients are loath to take advantage of their facilities. General hospitals, particularly large municipal hospitals, are constantly called on to receive such patients and to keep them for long periods, pending their final placement in suitable institutions. During this time, these open cases of tuberculosis are in many ways similar in their contagiousness to other cases of the more acute infectious diseases. Arrangements for their management should be adequate to minimize the spread of disease among the hospital contacts, and such arrangements are nowise different from those necessary for the care of patients with other communicable diseases.

Another factor to be taken into account, particularly in this part of the country, is the steady increase in the burdens that the general hospitals are carrying. All physicians in large cities are constantly troubled with the inability to obtain hospital facilities for those among their patients who require care that cannot be given in the home. The overcrowding of these hospitals is due, in large measure, to the increase in popularity of the agencies that provide hospitalization insurance. In the future it is to be expected that hospital insurance will become more rather than less popular and that the burden on the general hospitals will consequently increase.

The specialized hospitals for contagious diseases, on the other hand, are not being used to capacity. Even during epidemics the use of their facilities is only temporary. The staffs of such hospitals are necessarily large, and a good part of the staff must be maintained even when this is not warranted by the number of cases. Furthermore, because of the wide fluctuations in use, their facilities are often permitted to deteriorate, and the aid of modern equipment and treatment, which is available in general hospitals, is often denied to patients.

The present problem of the shortage of nurses may provide a good excuse for the immediate consideration of this important problem. Contagious-disease hospitals require a relatively greater number of nurses per patient than do general hospitals and much of the time a large percentage of these nurses are not working to capacity; general hospitals, on the other hand, are much understaffed and their nurses are greatly overworked.

The objection that provisions must be made for the emergencies incident to epidemics does not provide an argument for the maintenance of special contagious-disease hospitals. General hospitals should be able to expand their facilities for the emergencies provided by disasters, and epidemics may well be classed in a group with other disasters. The reorientation of existent communicable-disease hospitals to serve within the framework of the general hospitals, although it might not entirely alleviate the nursing and bed situation, would undoubtedly be of some help. The views of the New York State Department of Health[2] on this subject have recently been summarized at the request of a group of hospital administrators and health officers and are worth quoting:

> In the early part of this century, there was a tendency on the part of municipalities to build special hospitals for the isolation of communicable diseases. These so-called "pest houses" were designed particularly for the care of smallpox cases but were intended for the isolation of other acute infectious diseases as well. At that time, it was thought feasible to control communicable diseases in communities through isolation of recognized cases since it was felt that if all patients were isolated until they were no longer infectious, the spread of these diseases would cease. However, upon further investigation from a bacteriological standpoint, it was learned that in many communicable diseases, symptomless carriers and atypical cases which ordinarily would not be recognized as infectious are frequently more important in the spread of the disease in the community than the typical cases which can be detected. The routine hospitalization of acute communicable diseases for the sole purpose of limiting spread of the infection in the community, therefore, obviously would not accomplish this objective.
>
> At present, hospitalization of contagious diseases ordinarily is recommended only in those cases requiring care from the standpoint of the welfare of the patient himself and which can be given only in a hospital and not at home. In rare circumstances, it may still be necessary to hospitalize patients from the standpoint of the protection of the community as, for example, in the case of a communicable disease discovered in a transient or occurring in a home in which for certain reasons proper isolation is impossible.
>
> Concomitant with the development of our bacteriological knowledge of communicable disease, techniques have been devised to permit the safe isolation of cases of communicable diseases in general hospitals. These procedures vary with the disease: some patients can be cared for without danger on a ward; others must be confined to a private room. However, there is essentially no communicable disease which cannot be cared for safely in a private room on a floor on which there are other patients with noncommunicable diseases, providing certain techniques are practiced rigidly by the attendants. It has become increasingly clear that the training and skill of the attendants are much more important in controlling the spread of infection than the physical equipment provided.
>
> In the opinion of the New York State Department of Health, therefore, separate buildings for the sole care of communicable diseases are not essential. In larger municipalities it may be more convenient for a hospital to have a separate building for this purpose but this is a matter of convenience and not necessity. In smaller places in which such a building would be vacant a large part of the time, an unnecessary expense to the community would be entailed.
>
> Every hospital is dealing with communicable diseases whether or not it recognizes that fact. Because of the prevalence of carriers and atypical cases among the general population, it is inevitable that such carriers and cases will be admitted from time to time to a hospital even though the infection is not detected at the time of admission. The routine procedures followed in these hospitals, therefore, with regard to the hygienic practices of the

attendants, the handling of food and dishes, and the use of various types of equipment (such as thermometers, enema apparatus, etc.) should be such that there is no likelihood of the transfer of secretions or excretions from one patient to another. If such techniques are not followed, sooner or later an outbreak is bound to occur through the introduction of pathogenic microorganisms by a carrier or atypical case.

These views, although expressed from the point of view of the physicians of upstate New York, are applicable to other localities in many parts of the country. In small communities where contagious-disease hospitals are idle most of the time while the general hospitals are overcrowded, this may be an appropriate time to consider the proper readjustments.

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CUSHING'S LIBRARY

Of the multiple interests of the late Harvey Cushing no one was more deeply imbedded in his personality than his love of books. Beginning as a student, he built up a library of nearly eight thousand volumes, a collection he bequeathed to Yale University. Certain sections of the library, having particular interest on account of their size or completeness, were to be catalogued by his request. In order to give a complete idea of the whole library, however, the Historical Library of the Yale Medical Library has issued a short-title catalogue[1] of all the books.

To those familiar with Cushing's taste in books, it is not surprising to find the incunabula section and the writings of Paracelsus, Paré and Vesalius filling many shelves. Indeed, one hundred and sixty-eight medical incunabula, with sixty manuscripts, comprise a collection that any medical library would be proud to own. Hardly half a dozen collections of this magnitude exist in America. In addition, Cushing owned over forty editions of books by Paré, sixteen by Paracelsus and more than fifty by Vesalius. The last, the only group carefully worked over by Cushing, have recently been considered in a special study.[2] Other authors, however, are also well represented: Robert Boyle, sixty-one editions; Nicholas Culpeper, one hundred and ten; Daniel Drake, sixteen; Robert Fludd, nineteen; Samuel Garth, twenty-four; William Harvey, forty-three; Edward Jenner, thirty; Leonardo da Vinci, eighteen; Carl von Linné, thirty-four; Silas Weir Mitchell, forty-three; William Salmon, twenty; and Tobias George Smollett, seven. The longer lists might be supplemented by many important shorter ones, some containing even greater books from the pens of less prolific writers. His contemporaries — Osler, Klebs, Welch, Power, Sarton, Singer and others — are naturally fully represented. Since the surgical texts and periodicals were removed from his library when Cushing left Boston in 1930, the books now catalogued represent those that he thought were worth saving, the result of years of collecting. If an individual library may be said to reflect the man, surely a portrait of Cushing stands out in the contents of this catalogue. Broad interest, complete details, sound universality but exact focal discrimination and "looking all around a problem," to use one of his favorite expressions — in other words, the characteristics of Harvey Cushing — are well mirrored in his carefully selected library.

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1. *The Harvey Cushing Collection of Books and Manuscripts.* Publication No. 1, Historical Library, Yale Medical Library. 207 pp. New York: Schuman's, 1943.
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MEDICAL EPONYM

Pellegrini–Stieda–Köhler Disease

Dr. Augusto Pellegrini, while an assistant in Burci's surgical clinic at Florence, described "Ossificazione traumatica del legamento collaterale tibiale dell' articolazione del ginocchio sinistro [Traumatic Ossification of the Ligamentum Collaterale Tibiale of the Left Knee Joint]" in *La Clinica Moderna* (**11**: 433-439, 1905). A portion of the translation follows:

> The ossification that I had the opportunity of studying developed in the ligamentum collaterale tibiale of the knee following an injury. It exhibits many similarities, both in etiology and pathogenesis as well as in its course, to the traumatic ossifications of muscle that are more commonly termed traumatic muscular osteomata. . . .

Professor Alfred Stieda (b. 1869), of Königsberg, reported "Ueber eine typische Verletzung am unteren Femurende [Concerning Typical Injury at the Lower Extremity of the Femur]" in connection with a demonstration at the Third Congress of the Deutsche Röntgengesellschaft at Berlin in 1907. This report appears in *Archiv für klinische Chirurgie* (**85**: 815-826, 1908). A portion of the translation follows:

> Anyone who works over a rather large number of surgical x-ray films must be struck by the occurrence of a small

bone shadow in pictures of knee injuries, which in dorso-ventral films is typically found on the tibial side, near the transition from diaphysis to internal condyle of the femur. This shadow lies close by the inner condyle of the femur, but is clearly separated from it by a translucent zone.

The position of the shadow, which is almost exactly similar in all films, is forthright evidence that this is always the same bit of bone, which has been broken off by external force or torn off by the pull of an attached structure, tendon or muscle.

Alban Köhler (b. 1874), of Wiesbaden, in his book *Die normale und pathologische Anatomie des Hüftgelenkes und Oberschenkels in röntgenographischer Darstellung* [*Normal and Pathologic Anatomy of the Hip and Femur as Shown by X-ray*] (Hamburg, 1905), describes Plate vii, Figure 12 (page 140), as follows:

> Ossifications in the region of the knee joint. . . . In the upper part of the external condyle at the juncture with the shaft, in the soft-tissue shadow, [is] a small, smooth, dark shadow . . . that can only be interpreted as an ossification of connective tissue.

This picture of Köhler's is referred to by Stieda in the above-quoted article.

R. W. B.

MASSACHUSETTS MEDICAL SOCIETY

REFUND DISTRIBUTION

The Treasurer of the Massachusetts Medical Society makes the following report regarding the refund to district societies for 1944:

The Council voted to distribute the sum of $4000 to district societies. The total number of payments of annual dues received by the Treasurer by March 1, to be counted for the refund, was 3060. Therefore the refund to the district societies for each paid fellow is $1.307.

The following table gives the number of payments, as of March 1, and the refund to each district as of April 1:

District	Number Reported Paid	Refund
Barnstable	31	$40.56
Berkshire	84	109.82
Bristol North	41	53.62
Bristol South	139	181.70
Essex North	128	167.33
Essex South	180	235.29
Franklin	29	37.94
Hampden	201	262.74
Hampshire	39	51.01
Middlesex East	80	104.59
Middlesex North	75	98.06
Middlesex South	620	810.37
Norfolk	503	657.45
Norfolk South	83	108.51
Plymouth	89	116.35
Suffolk	428	559.43
Worcester	251	328.09
Worcester North	59	77.14
	3060	$4000.00

In 1943, for comparison, the total number of payments for the refund was 3466.

Eliot Hubbard, Jr., M.D., *Treasurer*

DEATH

MANNIX — Louis E. Mannix, M.D., of Chicopee, died March 11. He was in his sixtieth year.

Dr. Mannix received his degree from Tufts College Medical School in 1908. He was a member of the staff of Mercy Hospital, Springfield, the Massachusetts Medical Society and the American Medical Association.

WAR ACTIVITIES

MASSACHUSETTS COMMITTEE ON PUBLIC SAFETY

Communicable Diseases in Time of War

The following is part of a statement recently issued by the Subcommittee on Communicable Diseases, Health Committee, Massachusetts Committee on Public Safety.

* * *

The committee has reviewed the experience with communicable diseases in Massachusetts during the past two years and has also considered the current situation and the possible impact of war and postwar conditions.

Sanitation. With the shortage of manpower, and especially because of the withdrawal of large numbers of physicians and nurses from community work into the armed services, the community health problems are more, rather than less, acute than they were two years ago. Over-all sanitary measures should be maintained at a high level of efficiency. Although the menace of damage by bombing to sewer mains or water supplies has probably disappeared, deterioration due to neglect or relaxation of vigilance in protection of water, milk and other supplies, owing to manpower shortage, may occur unless the community is fully aware of the dangers.

Local communities are now studying worthwhile postwar public-works projects and it is entirely appropriate to include new installations or the extension of existing public sewer systems, the extension of public water supplies, where necessary, and the completion of drainage projects and other sanitary works that will benefit the community and promote public health.

Immunization practices. The committee cannot urge too strongly the importance of continuing, or improving on, programs for immunization against communicable diseases for which such procedure had proved to be effective and safe. Again, we point out that the burden on the physicians serving our communities has increased enormously and that their chief concern must be primarily with the care of the sick. Although we believe that it is, and should be, the primary function of private physicians to immunize babies and young children who are directly under their care and to immunize adults, especially against smallpox where necessary, we believe that in this emergency greater clinical facilities for immunization should be offered. A much greater efficiency can be obtained by immunization of large numbers of people at clinics than can be accomplished by private practice in the home or office.

Diphtheria toxoid. It has been repeatedly shown that any community neglecting to keep a high proportion of preschool children immunized against diphtheria runs a serious risk of an occurrence of this disease. We, therefore, recommend that every effort be made to provide public clinics for immunization of children, as soon after the age of seven months as possible, by the administration of toxoid provided without cost by the State Department of Public Health. Unless these clinics have been continuous in the community, the same protection should be offered to children of school age.

Smallpox vaccination. Although the record in Massachusetts is probably unequaled as regards the absence of smallpox among its inhabitants, for the reasons stated in our earlier communication, this disease is still a genuine menace owing to the great mobility of our population and the frequent intercourse with foreign lands. Although vaccination against smallpox should be done at the earliest possible age, it is also most desirable that adults who have never been vaccinated, or who have not been vaccinated for many years, should receive prophylaxis. The law requiring children entering public schools to be vaccinated before admission should be vigorously enforced, but it is far more desirable that vaccination be administered earlier in life than the year previous to admission to school. It is also recommended that vaccination be performed between the months of September and June rather than in midsummer.

Whooping-cough vaccine. The committee believes that the recent experience with whooping-cough vaccine is sufficiently satisfactory so that it can now recommend that this immunization be performed in public clinics. It is more urgent with this disease that protection be given between the ages of six months and a year than

with any other disease, since whooping cough is most serious and fatal in infancy, and no immunity is inherited from the mother.

Tetanus toxoid. The experience with immunization against tetanus by the use of toxoid continues to be impressively favorable. With the reduced probability that large numbers of civilians will be wounded as a result of bombing, we believe that the need for mass inoculation of people is unnecessary. In private practice it is common and desirable that toxoid shall be administered to young children, and for any adults who are engaged in especially hazardous trades in which the risk of injuries is unusually high it may be desirable.

Typhoid vaccine. The committee's position in regard to vaccines against typhoid and paratyphoid infections is the same as previously stated — namely, that it is unnecessary in general practice but that those who may be subject to undue exposure should receive these prophylactics. Also in case of the accidental contamination of public water supplies the use of typhoid vaccines is recommended.

Combined vaccines. It is entirely practicable to administer two vaccines or prophylactic agents at one time. Common combinations are diphtheria toxoid and whooping-cough vaccine, and diphtheria and tetanus toxoid. The use of the former combination may well be considered for public clinics, but only for children under the age of three years.

Emergency care of communicable diseases. In view of the excess prevalence of upper respiratory infections, much of it influenza, in recent months, we urge local committees again to review the facilities that are available for care of the sick in the event of a widespread and devastating epidemic. So large a proportion of physicians and registered nurses have been taken from our communities by the armed services that an added burden is placed on those who remain. There is a reservoir of registered nurses and practical nurses, who have withdrawn from active practice on account of age or on account of being married, that can be canvassed for volunteer service in the event of an epidemic. Likewise, in many communities, there are a number of women trained in Red Cross home nursing who may be recruited as volunteers to go into homes and perform simple services that will be essential if whole families are stricken with illness at the same time.

Summary. The withdrawal of physicians and nurses from communities and the consequent more limited service, make it more imperative than ever that all those measures that may prevent sickness be employed in even greater intensity. The need for public clinics is greater than ever before to relieve private practitioners partially of the burden of giving prophylactic inoculations. Since our last communication the experience with whooping-cough vaccination has advanced to a point where we now recommend its universal use in children before one year of age. Also, the growing experience with the use of combined injections of antigens justifies their use on a clinical basis, reducing by half the necessary number of inoculations. The danger of a devastating epidemic of influenza, or of some other disease, is still a possibility and this eventuality should be provided for. Local communicable-disease committees have an important service to perform in creating public opinion in support of sound health practices, and in backing up or urging local boards of health, visiting nursing associations, hospital outpatient clinics and other organizations to participate in immunization programs.

CORRESPONDENCE

COST OF BLOOD-SUGAR TESTS

To the Editor: The cost of blood-sugar tests is often a bar to the accurate diagnosis and good treatment of diabetes. This is of importance because of the disclosure of a far greater number of diabetic persons living among us than we supposed, as brought out in an article in the December 9, 1943, issue of the *Journal*.

Few patients can afford to pay $5 for a blood-sugar test and, in addition, a fee for medical advice. The cost of performing a test for blood sugar really is considerable for a single test, but if several are run together the expense is far less. This is recognized and adjusted for in the laboratories of large hospitals where an isolated test is seldom carried out but, instead, groups of blood-sugar tests are made at one, two and three different times of the day. Any housewife knows that if five loaves of bread are to be baked, it is far easier to bake them all together than at five-hour intervals.

In one hospital in Massachusetts an excellent plan has been adopted by which *on one morning each week* blood-sugar tests are done for $1 and at other times at a larger fee. Indeed, years ago I learned from a woman physician in Miami that one laboratory there had a "bargain blood-sugar day."

I often urge my patients to inquire at hospitals or laboratories, to which they are sent for a blood-sugar test by their physicians, whether they cannot come at some special hour or day of the week when there is a reduced rate, and also whether they can buy a book of blood-sugar tickets good for a year and thus secure the advantage of wholesale charges.

I suppose it is an understatement to say that a technician can perform twenty blood sugar tests in a day and send the reports of the same to the patient or physician.

ELLIOTT P. JOSLIN

81 Bay State Road
Boston

RESTORATION OF LICENSE

To the Editor: This is to advise you that the certificate of registration in Massachusetts of Dr. John A. Carter, 24 Page Street, Malden, which was revoked October 17, 1940, was restored to him at the meeting of the Board held March 17, 1944.

H. QUIMBY GALLUPE, M.D., *Secretary*
Board of Registration in Medicine

State House
Boston

WHY DOCTORS HAVE CORONARY THROMBOSIS

To the Editor: The winter term of school is almost over. In two days peace will reign again. The sun will shine, the buds will burst (if the thermometer ever gets above zero), and I shall be able with tranquil heart to view the moon and stars and breathe the balmy air of spring under a New Hampshire heaven.

The nurse at the school has me licked, beaten to a frazzle, knocked over the ropes. I live in a state of terror and apprehension. If I were an excitable doctor and gave her any encouragement, the infirmary would be full all the time. There would be a steady procession to the hospital of the children, and it would require the full-time work of three or four physicians and surgeons. It would be a nurses' and physicians' paradise. Telegrams would be going out to all parts of the country. Parents would be arriving constantly by airplane, train and motor car. There would be fractured skulls and broken necks, dozens of cases of appendicitis, pneumonias, meningitis, typhoid fever, embolism, paralyses, epilepsy, contagious diseases of all kinds, failing heart and shock (fully half the children have been in "shock" at one time or another). I know about the last condition, because I am almost in it myself.

If such a state of affairs existed, this nurse's dream would have come true. She would live in the seventh heaven of bliss. The atmosphere would be charged with rumor, terror and suspense. She would hover over the "desperately ill" and the dying. She would be the ministering angel; she would be the "Lady with the Lamp." It matters not to her that she never learns by experience, that no mistake ever fazes her. She dramatizes disease as a great actor does his part. The telephone wires burn with messages. The operators must be in a continual state of jitters from the "urgent" (every call is urgent) calls directed at my office or house, day and night. Of course I never believe a word she says over the telephone, but there is always that infinitesimal chance that she may be right. I never know and so I live in mortal fear. The other day after diagnosing five cases of measles in five perfectly healthy children with no fever, cough, rash or sore throat (one case of measles had occurred at the school two weeks previously, so we were expecting some more, although we had administered placental extract), she called me up three times within five minutes in the middle of office

hours to tell me that a boy was having convulsions. He had broken his ankle three days before, and she suggested that he might have had an embolus to explain the convulsions. She said his respirations were 58 and his pulse rate 60! Leaving several patients in the office I dashed to the school at sixty miles an hour to find the boy asleep and, when waked up, totally oblivious that anything was wrong with him. His pulse was 76 and his respirations were 16. I became incoherent, and if I said anything it was only to mention the name of the deity over and over. After she saw that I was unsympathetic to the embolism theory, she suggested it might be epilepsy. I tore my hair again, but it did no good.

A few days later she again called me up — "urgently" — to tell me that a boy whose ankle I had strapped had suffered "agonizing pain" all night, that the strapping had caused great swelling and that he had paralysis of the foot and ankle. She had me worried, because I did not believe that she knew enough to make up such a story. I had visions of meeting the boy's parents face to face and trying to explain how I had not caused the paralysis, how these things happen once in a while, and how extremely unfortunate it was. I was willing to admit that perhaps I had put on the strapping a little too tightly. So in an agonized frame of mind I made my way to the school to find a foot that was normal in every respect except for the swelling caused by a badly sprained ankle.

A while ago there was a measles epidemic. Every day there were three or four new cases. Toward the end of the epidemic the nurse became tired and nervous, and her mind, which normally was extremely excitable, had reached the explosive stage. While walking with her across the campus, she told me she had found a dead rat. I did not say a word. I knew what was working in her mind. Sure enough, the next day the wires began to burn again, and after paging me over the countryside, she at last got me on the telephone. "There are two more down," she said, "I don't like it; I don't like it. I think you ought to come to the school immediately." I took my time in getting there, and on arrival found that another doctor had preceded me. I asked her what all the excitement was about. She wouldn't tell me, but I knew. She had made the diagnosis of bubonic plague!

And so I live from day to day, almost in a state of collapse, with the sword of Damocles hanging by a thread above my neck.

N. C. S.

NOTICES

BOSTON SOCIETY OF BIOLOGISTS

A meeting of the Boston Society of Biologists will be held at the Surgical Amphitheater (3A) of the White Building, Massachusetts General Hospital, on Wednesday, April 19, at 8 p.m.

PROGRAM

The Physical-Chemical Properties of the Plasma Proteins and Their Concentration into Fractions of Differing Functions. Drs. E. J. Cohn, L. E. Strong, J. L. Oncley, W. L. Hughes, Jr., and S. H. Armstrong, Jr.

Fibrinogen and Thrombin and the Products Derived from Them. Drs. J. D. Ferry, J. T. Edsall, E. A. Bering, Jr., and P. R. Morrison.

Immunological Studies on the Plasma Proteins. Dr. J. F. Enders.

Clinical Investigations with Albumin and Immune Globulins. Drs. C. A. Janeway, L. Woodruff and C. Ordman.

Clinical Investigations with Products of Fibrinogen and Thrombin. Drs. O. T. Bailey and F. D. Ingraham.

SOUTH END MEDICAL CLUB

The next regular meeting of the South End Medical Club will be held at the headquarters of the Boston Tuberculosis Association, 554 Columbus Avenue, Boston, on Tuesday, April 18, at 12 m. Dr. Vlado A. Getting will speak on the subject, "Tropical Diseases."

Physicians are cordially invited to attend.

MASSACHUSETTS CENTRAL HEALTH COUNCIL

Featuring a panel entitled "Should Social Security Be Extended Farther into the Fields of Medical Care and Hospital Service?" the annual meeting of the Massachusetts Central Health Council will be held at the Pioneer, Y.W.C.A., 140 Clarendon Street, Boston, promptly at twelve noon on Friday, May 5. After a buffet lunch (80 cents) and a brief business meeting, the panel discussion with the president, Dr. George C. Shattuck, acting as chairman, will proceed with the following leaders: Allan Butler, M.D., Massachusetts General Hospital; Alton A. Linford, A.M., assistant professor of social economy, Simmons School of Social Work; Gerald F. Houser, M.D., first assistant director, Massachusetts General Hospital; and Walter G. Phippen, M.D., member of the Massachusetts Medical Society.

Nurses and social workers, as well as physicians, are cordially invited to attend. Luncheon reservations should be sent to the secretary, Arthur J. Strawson, 1148 Little Building, Boston 16.

NEW ENGLAND SOCIETY OF ANESTHESIOLOGY

The next meeting of the New England Society of Anesthesiology will be held in the Bigelow Amphitheater of the Massachusetts General Hospital on Tuesday, April 11, at 8 p.m. Dr. K. M. Heard will speak on the subject, "Benefits and Hazards of Pentothal."

NEW ENGLAND DERMATOLOGICAL SOCIETY

The annual meeting of the New England Dermatological Society will be held in the Skin Out Patient Department of the Boston City Hospital on Wednesday, April 12, at 2 p.m.

NEW ENGLAND OPHTHALMOLOGICAL SOCIETY

A meeting of the New England Ophthalmological Society will be held at the Massachusetts Eye and Ear Infirmary, 243 Charles Street, Boston, on Tuesday, April 18, at 8 p.m.

Following the business meeting, John Marquis Converse, a major in the Medical Corps of the French Army, will show a motion picture. Dr. Walter B. Lancaster will then speak on the subject "Some Chestnuts from My Stock Pile."

NEW ENGLAND OTO-LARYNGOLOGICAL SOCIETY

The regular spring meeting of the New England Oto-Laryngological Society will be held at the Massachusetts Eye and Ear Infirmary on Wednesday, May 10.

NEW ENGLAND PATHOLOGICAL SOCIETY

The annual meeting of the New England Pathological Society will be held at the Harvard Club, Boston, on Thursday, April 20. Following the dinner at 6 p.m., Dr. Tom Spies will speak on the topic, "Pathological Changes Occurring in Certain Vitamin Deficiencies in Man."

UNITED STATES CIVIL SERVICE COMMISSION

While on battlefronts scattered throughout the world our Armed Forces are concentrating on winning the war, in Army and Veterans' hospitals here in the United States, trained occupational therapists are among those bending their efforts toward winning the peace.

These therapists are erasing the ravages of war by the systematic rehabilitation of injured bodies and minds. Some

of the war-wounded are reconditioned for further service in the Army; others are fitted for useful civilian work in a normal environment.

As increasing numbers of injured soldiers return to the hospitals, more and more occupational therapists are needed to aid in their adjustment to normal life. In greatest demand are experienced graduates of accredited schools of occupational therapy. Experience should be in hospitals acceptable to the American Medical Association. For some positions, however, college training in psychology and in arts and crafts or trades and industries, or experience as a junior aide in Veterans' hospitals, may be substituted for training in occupational therapy schools. Other positions will be filled by inexperienced graduates of occupational therapy schools.

The salary range of these positions is $1970 to $2433 a year, including overtime pay. Those appointed at $1970 will be trainees for a period of eighteen months; those appointed at $2190 and $2433 will administer occupational therapy under medical and general supervision in Army and Veterans' hospitals.

There are no age limits and no written tests, but applicants must be physically capable of performing the duties involved. Persons now using their highest skills in war work should not apply. Federal appointments are made in accordance with War Manpower Commission policies and employment stabilization programs.

Further information on occupational-therapy aide positions and forms for applying can be obtained from first-class and second-class post offices or from the United States Civil Service Commission, Washington 25, D. C.

SOCIETY MEETINGS AND CONFERENCES

Calendar of Boston District for the Week Beginning Thursday, April 13

Thursday, April 13

*9:00–10:00 a.m. Medical clinic. Dr. S. J. Thannhauser. Joseph H. Pratt Diagnostic Hospital.

Friday, April 14

*9:00–10:00 a.m. Treatment of Amputees in the Services and Later. Rear-Admiral R. H. Laning (MC), U.S.N.R. Joseph H. Pratt Diagnostic Hospital.

Saturday, April 15

*10:00–11:30 a.m. Medical staff rounds. Peter Bent Brigham Hospital.

Monday, April 17

*12:15–1:15 p.m. Clinicopathological conference. Peter Bent Brigham Hospital.

Tuesday, April 18

*9:00–10:00 a.m. Medical clinic. Dr. S. J. Thannhauser. Joseph H. Pratt Diagnostic Hospital.

*12:00 m. Tropical Diseases. Dr. Vlado A. Getting. South End Medical Club. Headquarters of the Boston Tuberculosis Association, 554 Columbus Avenue, Boston.

*12:15–1:15 p.m. Clinicoroentgenological conference. Peter Bent Brigham Hospital.

Wednesday, April 19

*12:00 m. Clinicopathological conference. Children's Hospital.
8:00 p.m. Boston Society of Biologists. Surgical Amphitheater (3A) of the White Building, Massachusetts General Hospital.

*Open to the medical profession.

April 11. New England Society of Anesthesiology. Page 443.

April 12. New England Dermatological Society. Page 443.

April 13. The Use and Misuse of Bacterial Chemotherapy. Dr. Charles A. Janeway. Pentucket Association of Physicians. 8:30 p.m. Haverhill.

April 18. New England Ophthalmological Society. Page 443.

April 20. New England Pathological Society. Page 443.

April 24 and 25. Massachusetts Safety Conference on War Production and Civilian Defense. Page ix, issue of March 30.

April 29. Long Island College of Medicine. Page ix, issue of March 30.

May 5. Massachusetts Central Health Council. Page 443.

May 8–14. War Conference on Industrial Medicine, Hygiene and Nursing. Page x, issue of March 23.

May 10. New England Oto-Laryngological Society. Page 443.

May 23 and 24. Massachusetts Medical Society. Annual meeting. Hotel Statler, Boston.

June 7–13. American Board of Obstetrics and Gynecology. Page x, issue of March 23.

June 12–16. American Medical Association. Annual meeting, Chicago. Page 798, issue of November 18.

June 12–16. American Physicians' Art Association. Page x, issue of March 2.

October 3–5. American Public Health Association, Hotel Pennsylvania, New York. Page ix, issue of March 30.

District Medical Societies

Suffolk

May 4. Censors' Meeting. Page xiii, issue of February 10.

Worcester

April 12. Hahnemann Hospital, Worcester.
May 10. Annual meeting.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

American Standard Definitions of Electrical Terms. 4°, cloth, 311 pp. New York: American Institute of Electrical Engineers, 1943. $1.00.

This authoritative reference work was compiled by a special committee representing thirty-three organizations in the electrical field and organized by the American Institute of Electrical Engineers. The committee was enlarged by the appointment of eighteen subcommittees with a total membership of one hundred and twenty, to which were added numerous nonmember experts, so that, in all, over three hundred authorities in all fields aided in the compilation. The primary aim of this glossary is to express for each term the meaning that is generally associated with it in electrical engineering in the United States. The preferred definition is a simple one, with a single statement of function rather than explicit description of all properties included and excluded. The arrangement is by special groups and subsidiary sections. The numbering used to identify terms is based on a system proposed for use by the International Electrotechnical Commission. Groups 75 and 80, having to do with radiology and electrobiology, including electrotherapeutics, are of medical interest. There is an extensive, comprehensive index. The work is well arranged and well printed on good paper in a good binding and sold at a nominal price. It should be in all medical libraries, as well as in the offices of all physicians interested in radiology and electrotherapeutics.

Lincoln–Douglas: The weather as destiny. By William F. Petersen, M.D. 8°, cloth, 211 pp., with 16 illustrations. Springfield, Illinois: Charles C Thomas, 1943. $3.00.

The author contends that the relation between the human body and the atmosphere in which it functions is of primary importance and that this relation must be understood if man is to make any progress in adjusting himself to the inexorable conditions of existence. His thesis has been built around the famous Lincoln–Douglas controversy.

Medical Clinics on Bone Diseases: A text and atlas. By I. Snapper, M.D. 4°, cloth, 225 pp., with 30 plates and 39 tables. New York: Interscience Publishers, Incorporated, 1943. $10.75.

In this book are presented observations and x-ray pictures especially chosen to elucidate some of the problems involved in the recent expansion of knowledge of bone diseases. The comparison of experiences is made between conditions in the Western Hemisphere and those in China.